

PHD

Studies towards the synthesis of functionalised 1,2,3,4-tetrahydroisoquinolines

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STUDIES TOWARDS THE SYNTHESIS OF FUNCTIONALISED
1,2,3,4-TETRAHYDROISOQUINOLINES

submitted by

ROSALIND H. STRANGE

for the degree of

Doctor of Philosophy

of the

University of Bath

1994

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Finally, my gratitude goes out to the SERC and Glaxo Group Research Ltd. for a CASE award.

(

For my mother and father.

SUMMARY

The work described in this thesis was carried out at the University of Bath between January 1989 and December 1991 and was initially concerned with the synthesis of topoisomerase inhibitors based on the plant alkaloid camptothecin.

However, the direction of research was changed and the majority of work is concerned with the preparation of functionalised 1,2,3,4-tetrahydroisoquinolines and their elaboration to pyrrolo, indeno and pentalenoisoquinolines.

A key process in this work is an intramolecular 1,3-dipolar cycloaddition step, to form two rings of a tetracyclic product in a single reaction.

Various intermolecular cycloadditions were also performed upon 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid to assess the reactivity of different dipolarophiles.

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INTRODUCTION

Cancer chemotherapy.

The aim of cancer chemotherapy is to spare normal tissue, whilst erradicating tumour cells in a manner that minimises the inherent drug resistance of such cells. Many anti-cancer agents operate by modifying the interaction of nuclear enzymes with DNA.

In most biological systems, DNA behaves as if it is topologically constrained. Regulation of DNA topology is of critical importance to normal cellular function. For example, if the amount of DNA supercoiling is diminished, this favours strand separation, which in turn facilitates DNA replication, gene transcription and transposition.

The principal means by which the cell controls the DNA topology is via a class of nuclear enzymes called Topoisomerases.^(1,2,3,4) These proteins act by introducing transient breaks in the phosphodiester backbone of the DNA. In eukaryotes, these enzymes are divided into two distinct groups based on their mode of action.

Type 1.

DNA Topoisomerase 1 (TOPO 1) is a 100 kilodalton monomeric protein derived from a single gene.⁽⁵⁾ It has the ability to break a single strand of duplex DNA, pass the intact DNA strand through the resulting gap, and

then reseal the broken strand. The enzyme remains bound at the 3' phosphoryl end of the break site via a covalent phosphotyrosine linkage during this process.(6,7,8) This linkage conserves the energy of the phosphodiester bond and facilitates rejoining. Hence the enzyme catalyses the relaxation of supercoiled DNA.(9) It has been shown to be especially important in the transcription of ribosomal RNA genes.(10,11,12,13)

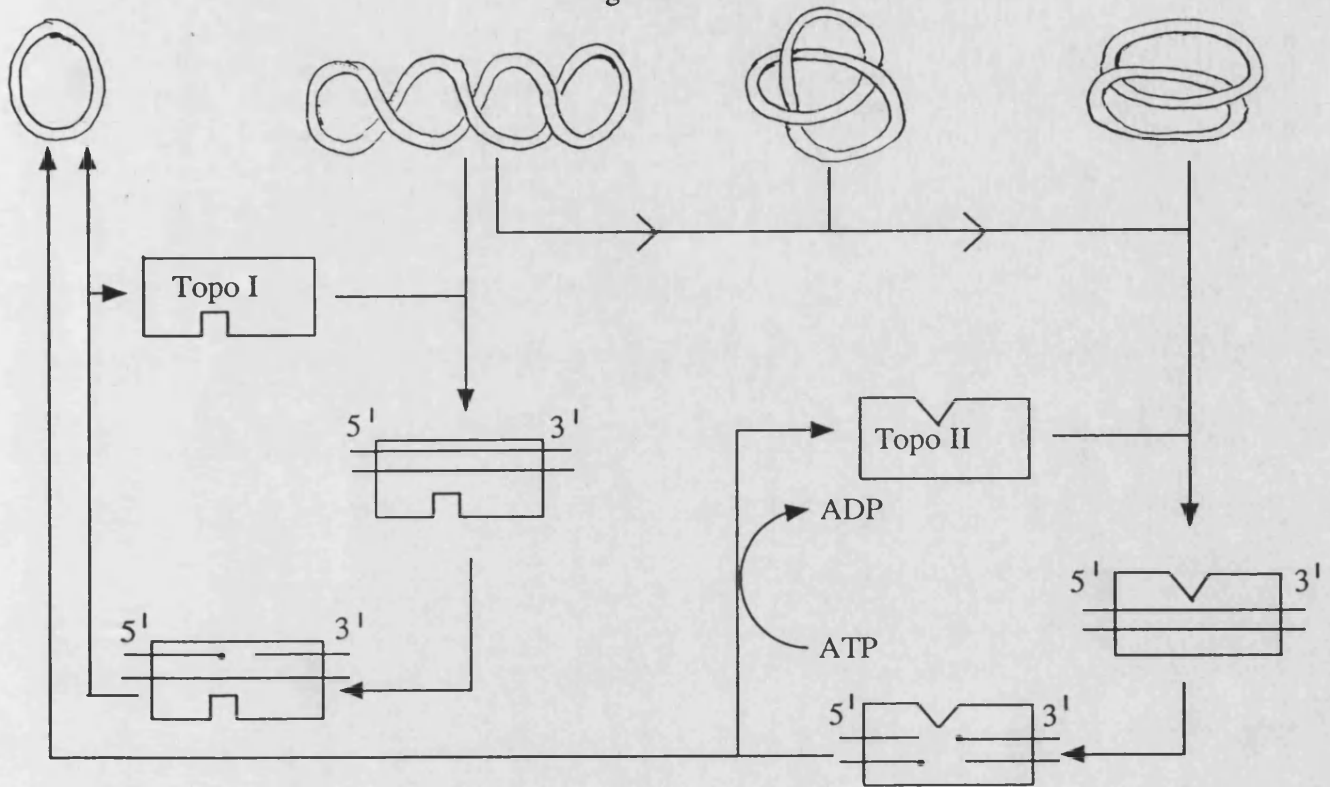
TYPE 2.

DNA Topoisomerase 2 (TOPO 2) is a dimeric 170 kilodalton protein, also derived from a single gene.(14) It is characterised by its ability to transiently break and reseal both strands of duplex DNA simultaneously, allowing the passage of a separate double helical strand through the break site during this process.

In contrast to TOPO 1, this enzyme remains bound to the 5' phosphoryl ends of the broken DNA strands.(15,16) Also, the strand passing activity of this enzyme is dependent on ATP hydrolysis.(17) Hence TOPO 2 can remove knots(18) and supercoiling in topologically constrained DNA. It can also reversibly catenate double stranded DNA circles.(19) Studies have shown the enzyme to be especially important in the separation of daughter chromosomes at the completion of replication.(20)

Diagrammatic representation of the role of the
topoisomerases.

Figure 1.



The first inference that topoisomerases might be involved in the action of anticancer drugs resulted from studies with the intercalating agents adriamycin and ellipticine.^(21,22) On exposure of mouse leukemia cells to these agents, unique protein-associated DNA breaks were observed. It was later shown by Liu that this covalently bound protein was in fact a topoisomerase.^(23,24,25) Liu's results also showed that, since a topologically restrained substrate was not required for drug-stimulated DNA cleavage, intercalation

with DNA by the drug was not necessary to effect cleavage.

Further studies with etoposide^(26,27) strengthened the hypothesis that DNA-drug binding was not a necessary requirement for topo-mediated DNA cleavage.

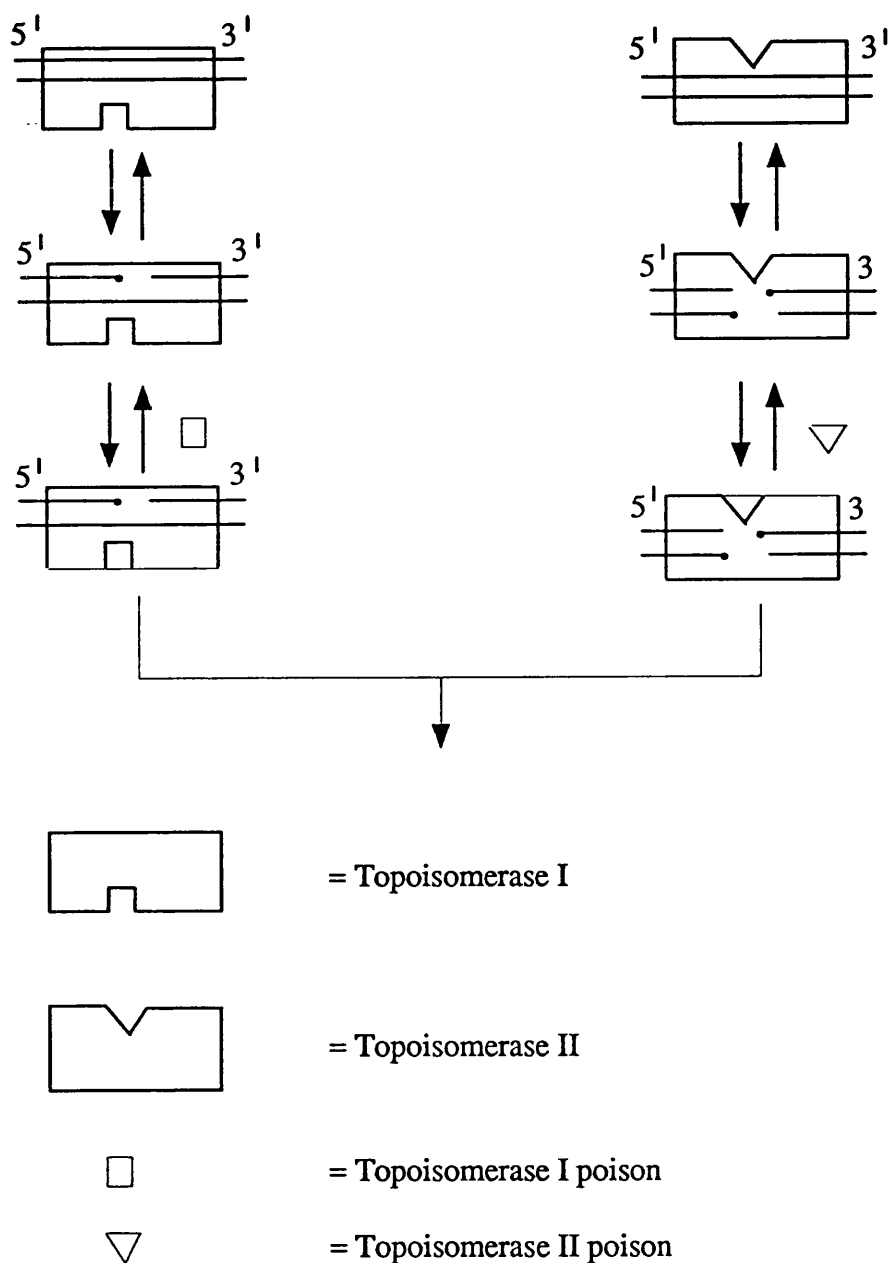
Research with agents such as ethidium bromide, which are effective at blocking the catalytic activity of topoisomerases, showed little topo-mediated DNA cleavage and only weak cytotoxicity. This suggested that topo-drug interaction alone is not sufficient for high toxicity.^(23,24,28,29,)

Further research supports the currently held view that these drugs act by stabilising the normally transient cleavable complex between DNA and topoisomerase.^(30,31,32,33,) The mechanism of cell death induced by DNA damage is still unclear. Some form of cellular processing of the drug-stabilised cleavable complex is required to trigger the lethal effect of topo poisons.^(34,35)

Interaction of these complexes with replication forks, helicases, proteases or nucleases has been suggested as being necessary to cause lethality.^(36,37)

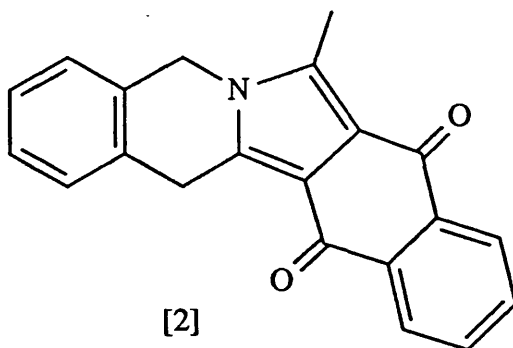
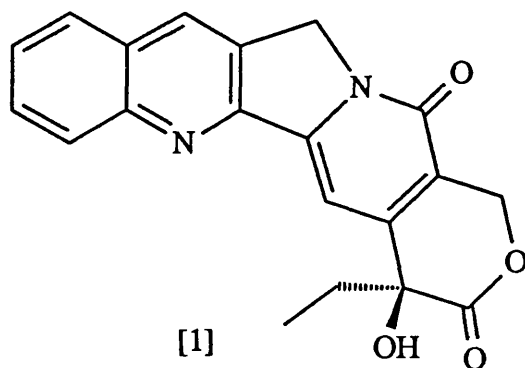
Figure 2.

diagrammatic representation of the mode of action of topo
poisons.



The topo 2 poisons⁽³⁸⁾ include a wide range of DNA intercalators. Among these, the acridines and anthracyclines have been studied most extensively.^(39,40,41) Two nonintercalative glycosidic derivatives of podophyllotoxins have also been shown to be topo 2 poisons.^(42,43)

The known topo 1 poisons on the other hand comprise a much smaller group, including camptothecin [1] and its derivatives and the pentacyclic isoquinoline-dione. [2]



Camptothecin.

The novel pyrrolo[3,4-b]quinoline alkaloid camptothecin [1] was first isolated by Wall et al. (44) from the chinese tree *Camptotheca acuminata* in 1966 as part of an antitumour screening program carried out by the National Cancer Institute. Extracts from the root and root bark displayed the highest activity. (45) Subsequently camptothecin has been isolated from various

plants in the Nothapodytes⁽⁴⁶⁾ and Merrilodendron genera of the Icacinaceae family, and also from the families Rubiaceae⁽⁴⁷⁾ and Apocynaceae.⁽⁴⁸⁾

Biogenesis of camptothecin.

The biogenesis of camptothecin has been the subject of extensive speculation and experimentation.⁽⁴⁹⁾ It was originally proposed that the compound was derived biosynthetically from a monoterpene indole alkaloid precursor by Wenkert.⁽⁵⁰⁾ Winterfield⁽⁵¹⁾ later expanded on this idea based on his finding that indole alkaloids underwent facile autoxidation in vitro to the pyrrole[3,4-*b*]quinoline chromophore.

Hutchinson⁽⁵²⁾ was the first to recognise the structural relationship between camptothecin and strictosamide [6]. Strictosamide⁽⁵³⁾ is formed from the cyclisation of strictosidine, [5], which is a key precursor for monoterpene indole alkaloid synthesis in a wide range of plant families. Strictosidine^(54,55,56) in turn is derived from a formal Pictet-Spengler condensation of tryptamine [3] with the monoterpenoid glucoside secologanin⁽⁵⁷⁾ [4]. Stereospecific incorporation of strictosamide into camptothecin has been confirmed using ¹³C labelled precursors⁽⁵²⁾.

Hutchinson proposed that the next step would be

the removal of glucose from strictosamide. However the isolation in 1989 of the quinolone [8] from an extract of *C. acuminata* showed this was not the case.⁽⁵⁸⁾ Instead the next step must be the oxidation-recyclisation of strictosamide via the 9-membered cyclic lactam [7]. A possible next step suggested by Hecht⁽⁵⁸⁾ is the isomerisation of the enol ether double bond to the endocyclic double bond shown in [9]. See figure 3.

Figure 3.

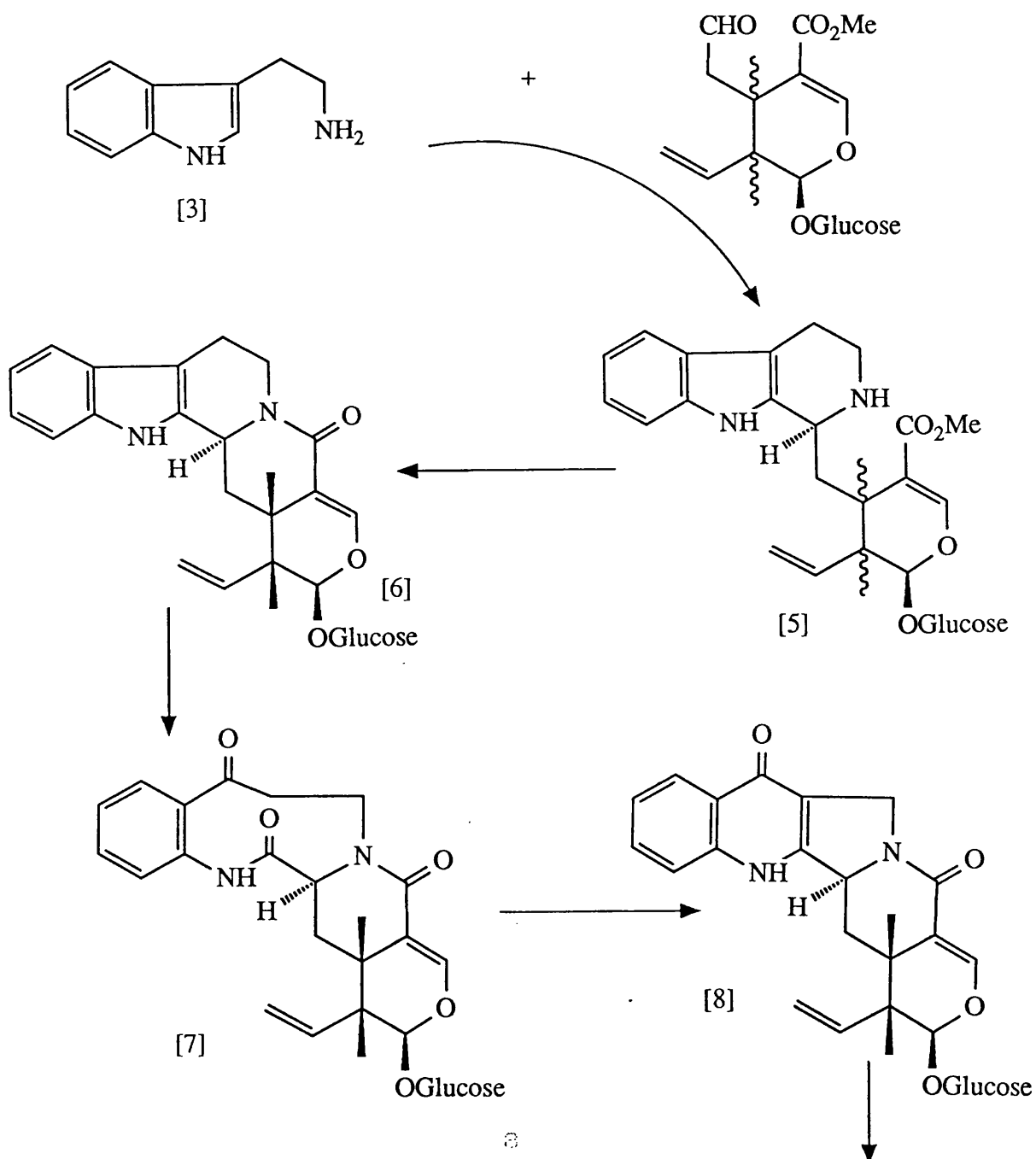
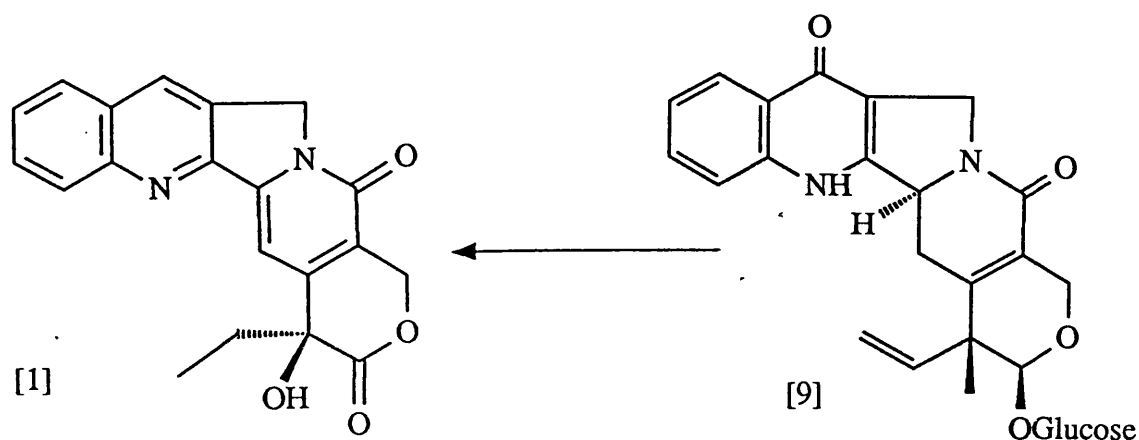


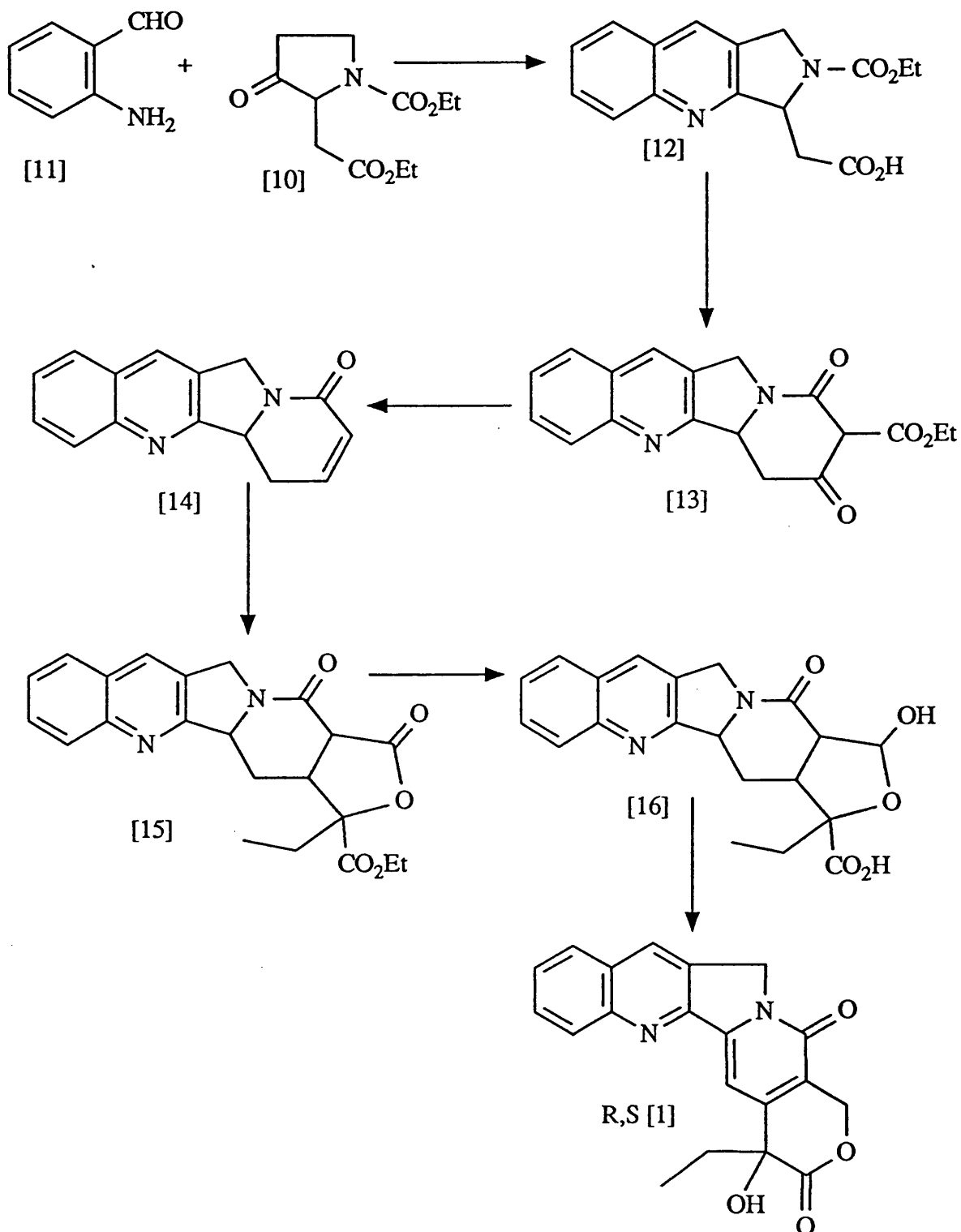
Figure 3 continued.



Synthesis of camptothecin.

The first total synthesis of camptothecin was achieved in 1971 by Stork and Schultz⁽⁵⁹⁾. Pyrrolidinone [10] was caused to undergo a base-catalysed Friedlander condensation with o-aminobenzaldehyde [11] to give the pyrrolo [3,4-b] quinoline acid [12]. This was subjected to a Dieckmann cyclisation to yield the tetracyclic β -ketoester [13]. Hydrolysis, decarboxylation and sodium borohydride reduction followed by elimination of water yielded the dihydropyridone [14]. This reacted with the lithium anion of a protected α -hydroxybutyric acid to give the pentacyclic lactone [15]. Ester hydrolysis and sodium borohydride reduction gave the hemiacetal [16]. Conversion to the acetate, oxidation with DDQ, acetate hydrolysis, reduction of the hemiacetal, followed by acidification led to racemic camptothecin in 1-2% overall yield. See figure 4.

Figure 4.



Only nine weeks later Danishefsky et al. reported the second total synthesis⁽⁶⁰⁾. This involved the addition of the amine [17] to dimethyl acetylenedicarboxy

late [18] to give the enamine [19]. This added in a Michael fashion to diethoxy carbonyl allene to yield the pyridone [20].

Transformation of this via a Dieckmann cyclisation of an intermediate tetramethyl ester gave the bicyclic [21]. Hydrolysis and decarboxylation of this, followed by a Friedlander cyclisation gave the tetracyclic [22]. Decarboxylation by pyrolysis over copper(II)oxide, followed by ethylation gave [23]. Addition of paraformaldehyde in acidic solution, followed by lactonisation, yielded 20-deoxycamptothecin [24]. This was oxidised to racemic camptothecin by treatment with hydrogen peroxide in alkaline solution. See figure 5.

Figure 5.

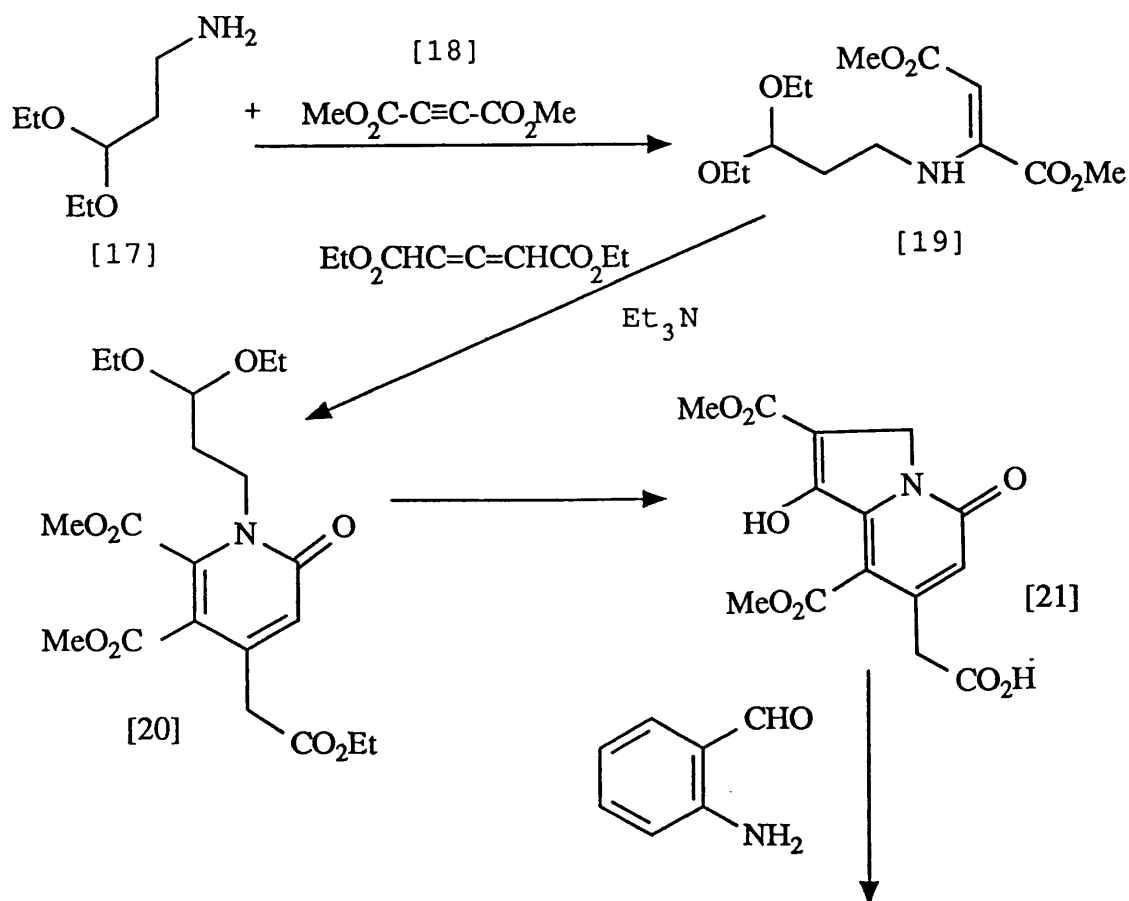
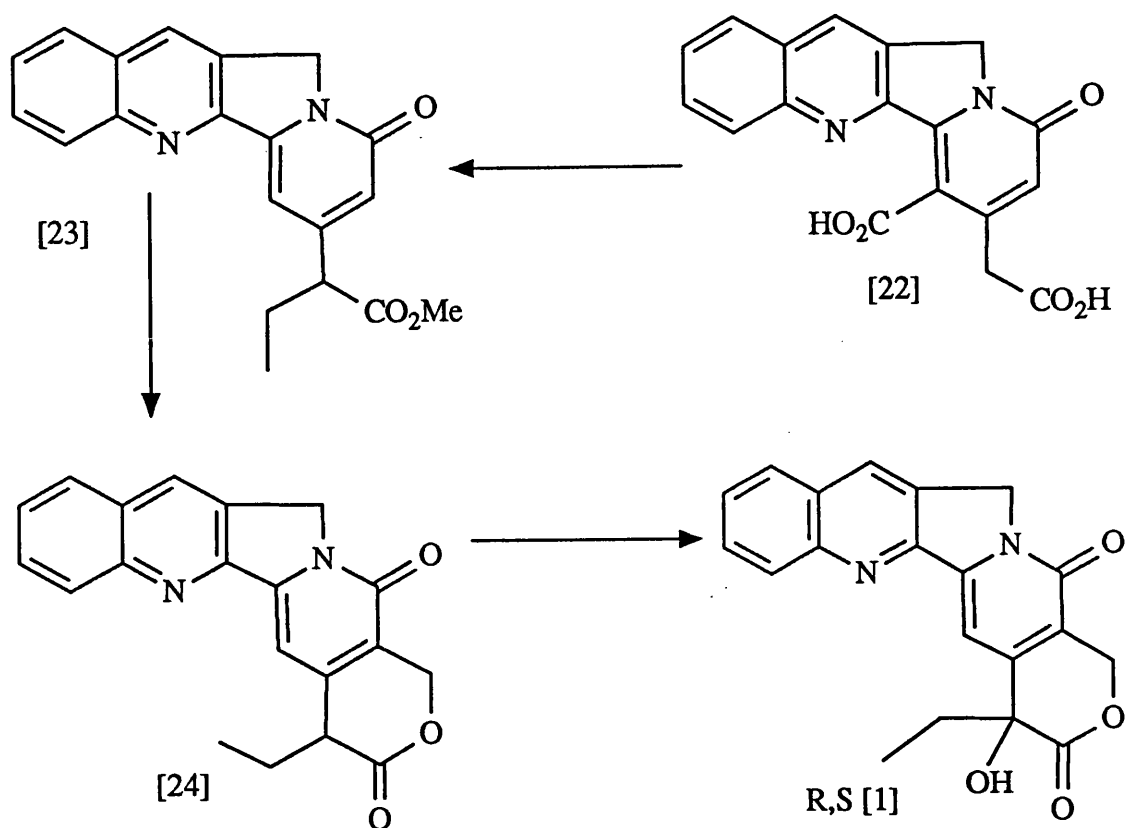


Figure 5 continued.



The first synthesis of chiral 20(S) camptothecin was reported by Corey's Harvard group in 1975⁽⁶¹⁾. This convergent synthesis combined the chiral pseudoacid chloride [31] with the tricyclic diamine [32], with the D ring being formed by cyclisation of an intermediate gamma-aldehyde-t-amide.

The 3,4-disubstituted furan [29] was resolved via its diastereomeric quinine salts and the tertiary alcohol protected as the carboxylate in the lactonised form. This gave product [30] in good yield.

Photooxidation of this furan followed by treatment with thionyl chloride in a catalytic amount of dimethylformamide gave a 2.5:1 mixture of [31] along

with its undesired regioisomer. This mixture was then condensed with the pyrroloquinoline [32] in pyridine acetonitrile to give the intermediate [33], which after base-catalysed condensation-cyclisation, gave the 20(S)-20-methoxycarbonyl [34]. Lithium mercaptide in HMPA cleanly deprotected [34] to give 20(S) camptothecin. See figure 6.

Figure 6.

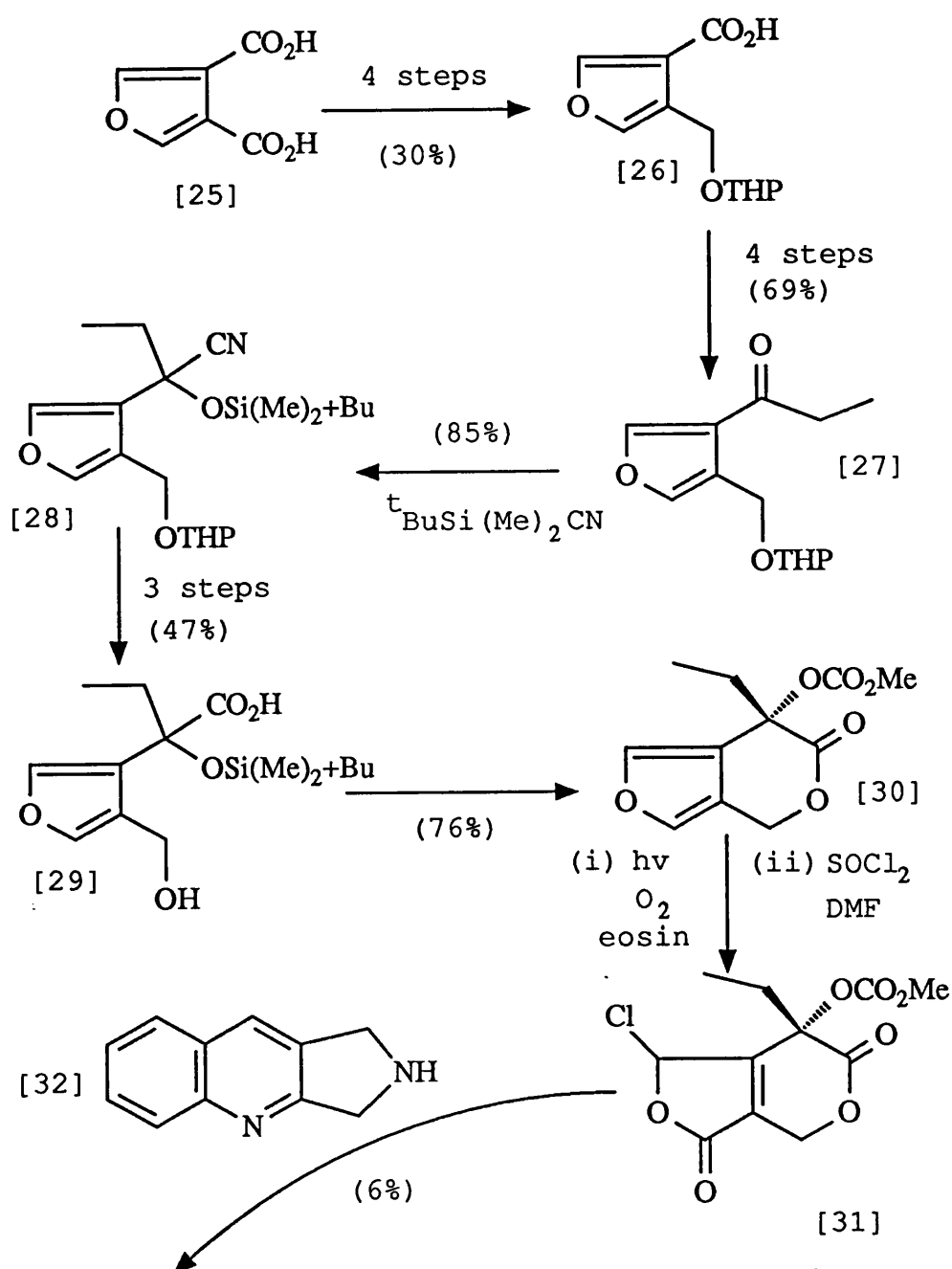
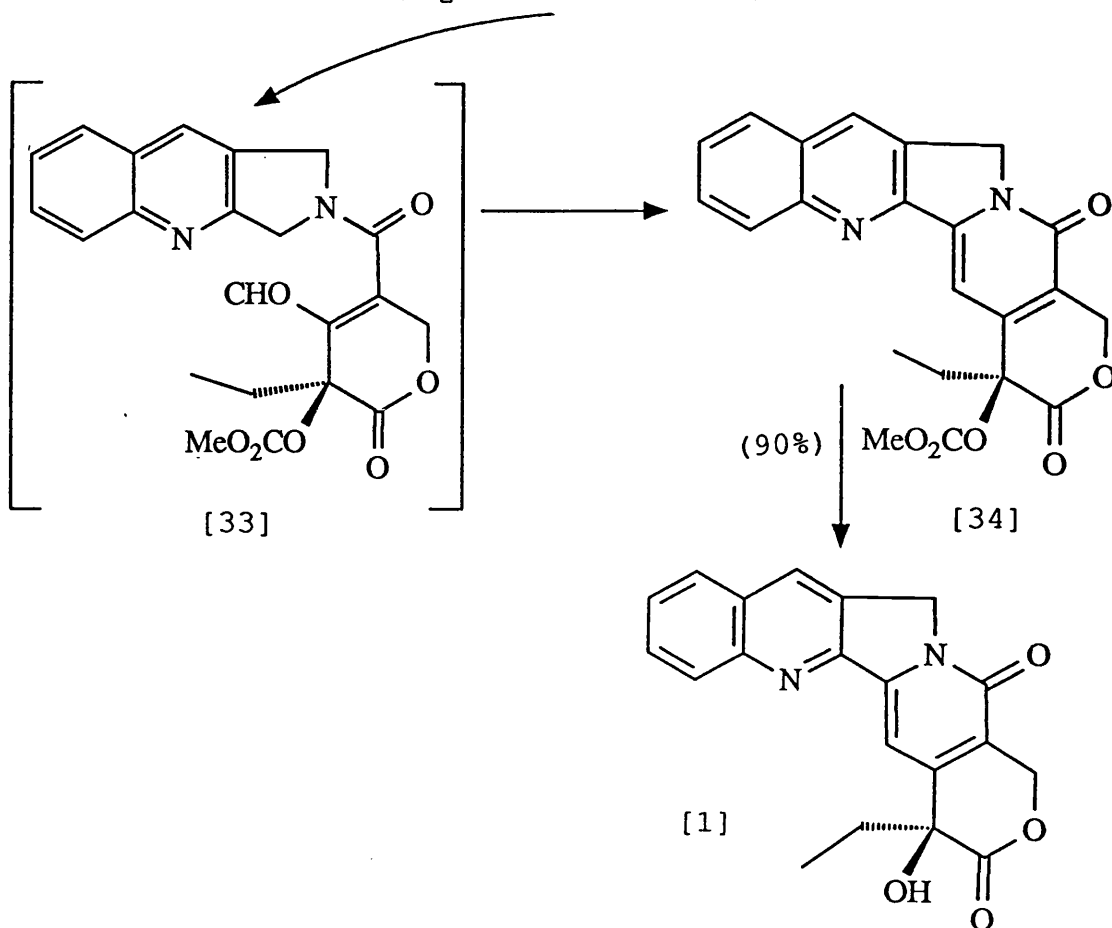


Figure 6 continued.



Medicinal Chemotherapy.

A correlation between the ability of camptothecin to induce DNA breakage and antitumour activity has been suggested from studies of camptothecin analogues⁽⁶²⁾. Also, the reports that camptothecin-resistant cells possess an altered topo I, that is not inhibited by the drug, support the hypothesis that camptothecin kills cancer cells by inhibiting this enzyme^(63,64,65).

Medicinally, camptothecin has been shown to exhibit antitumour activity in several experimental lines⁽⁶⁶⁾. These include human lung, mammary and colon tumour lines^(67,68). At present the compound is only used medicinally in China, where it has been shown to be

successful against liver carcinomas and tumours of the head and neck⁽⁶⁹⁾.

The toxicity of camptothecin however is a major deterrent to its more widespread use in the treatment of human neoplasia⁽⁷⁰⁾.

1,3-Dipolar cycloaddition.

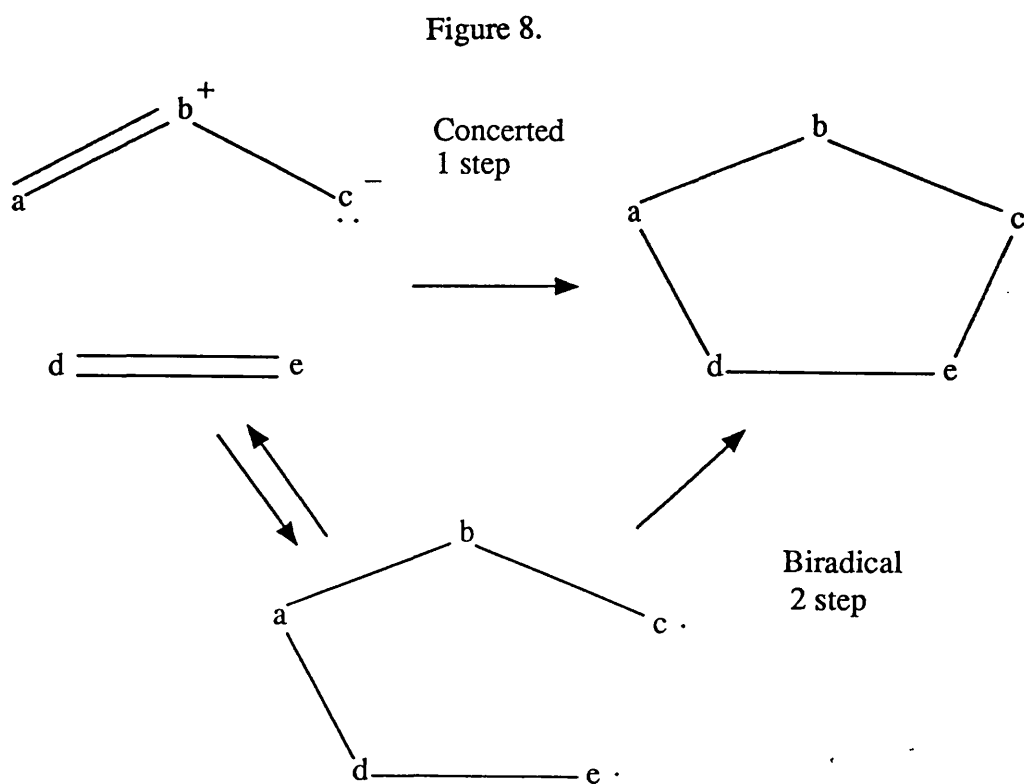
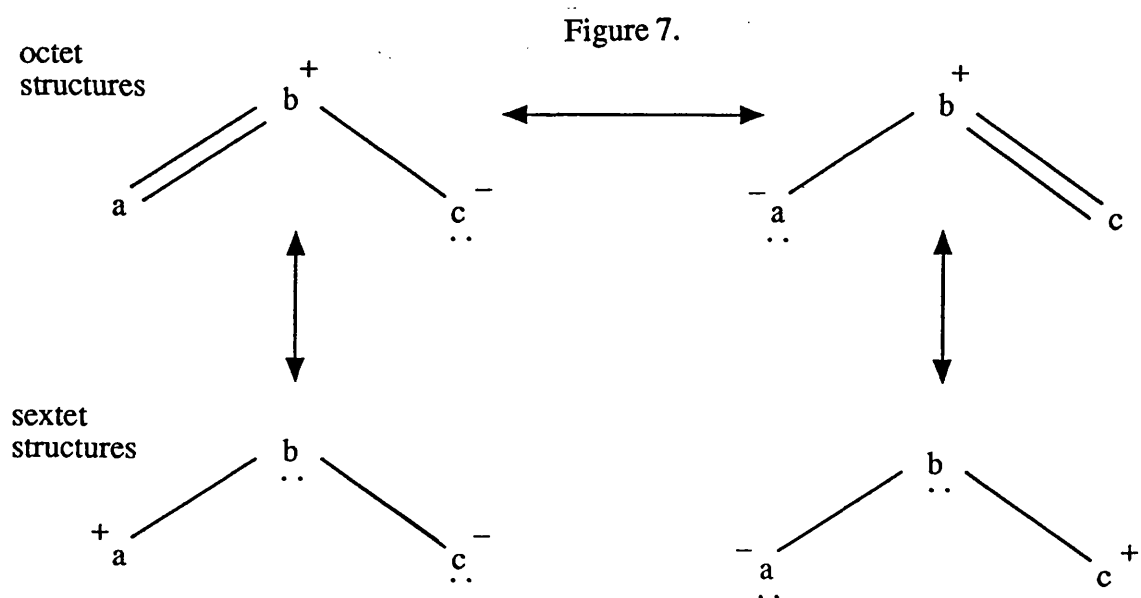
The addition of a 4 pi-electron-3-carbon system to a pi bond is known as a 1,3-dipolar cycloaddition reaction. In contrast to the Diels-Alder reaction, which has attracted much attention from the 1930's onwards, 1,3-dipolar cycloaddition was not systematically investigated until the late 1950's, even though the first example of this reaction was first described in 1888⁽⁷¹⁾.

The 1,3-dipole is an allyl-anion type pi system, with four electrons in three parallel atomic orbitals. The three atoms can consist of a wide variety of carbon, nitrogen and oxygen combinations. The dipolarophile can be a double or triple bond.

The term 1,3-dipole can be misleading since not all of these compounds show high polarity. The 1,3-dipole can be represented by two resonance structures. One, in which both terminal atoms possess a full octet of electrons and the positive charge is located on the central atom. Alternatively, the electrophilic centre can be localised on one of the terminal atoms, creating a sextet of electrons on that atom. See figure 7.

In the 1960's much attention was focused on whether the mechanism proceeded in a concerted fashion or

through a biradical intermediate. The two main protagonists in this debate were Rolf Huisgen, who published much evidence in support of a concerted mechanism^(72,73,74) and Ray Firestone, who advocated a biradical approach to the mechanism^(75,76,77). See figure 8.



The high stereospecificity observed in the cycloadditions of 1,3-dipoles with cis-trans isomeric dipolarophiles tends to argue against the biradical approach^(78,79,80,81). Firestone counters this problem with the hypothesis that in the intermediate biradical, the activation energy for ring closure, or reversion to reactants, is less than the energy barrier to rotation.

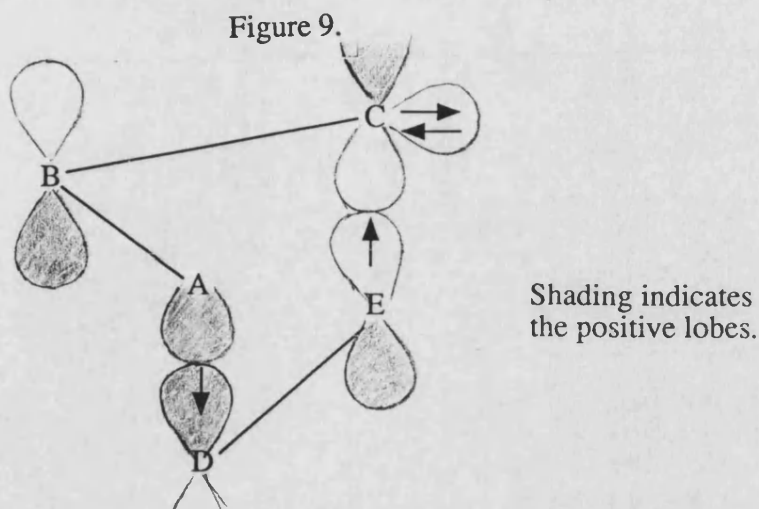
However, work with other known biradicals has shown a high degree of stereoequilibration in these types of reactions⁽⁸²⁾. Also, oxy radicals, such as those formed in the cycloaddition of nitrones are notorious for their hydrogen affinity, yet no hydroxylamine type side products have been observed in these reactions^(83,84,85).

The current view⁽⁸⁶⁾ is that the mechanism is a concerted one with simultaneous, but not necessarily synchronous, bond formation and breakage.

The mechanistic scheme for a concerted 1,3-dipolar reaction fits the selection rules devised by Woodward and Hoffmann for cycloadditions⁽⁸⁷⁾. The reaction is thermally allowed and the two reactants approach each other in a suprafacial manner.

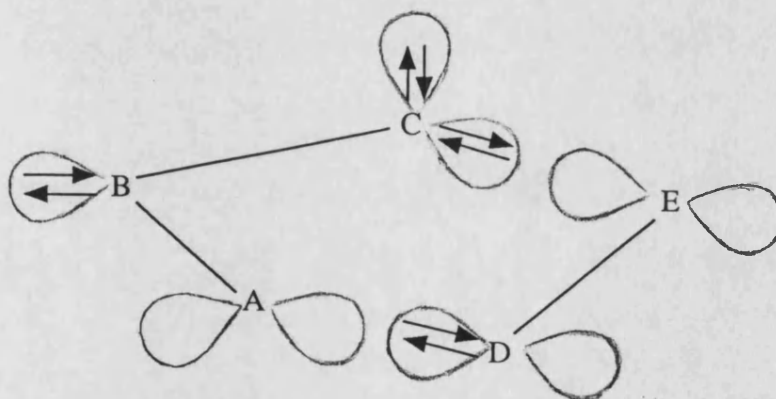
Thus the dipole (ABC) and the dipolarophile (DE) approach each other to form a two plane orientation

complex. See figure 9.



This assembly has the advantage over the all planar arrangement in figure 10 in that the A=B pi bond does not have to be sacrificed and hence allyl resonance is maintained for as long as possible⁽⁸⁸⁾.

Figure 10.



The pi orbitals of the terminal atoms of the dipole must bend slightly inwards to make contact with the pi orbitals of the dipolarophile, which bend outwards slightly. Gradual rehybridisation ensues, turning the terminal p orbitals of the dipolarophile into sp^3 orbitals which form the new sigma bonds. This is accompanied

by an uplifting of the middle atom B, the former p orbital of which, contains the unshared electron pair after the process is finished.

Regioselectivity in 1,3-dipolar cycloadditions.

In order to determine the regioselectivity of these reactions, it is necessary to look at the molecular orbitals on the reactants.

The energy gain obtained upon combining orbitals on separate reactants is inversely proportional to the energy difference of the combining orbitals.

The most important interactions are therefore between the highest occupied molecular orbitals (HOMO's) and the lowest unoccupied molecular orbitals (LUMO's), since they possess the smallest energy separation.

The special role of these frontier molecular orbitals was first recognised by Fukui⁽⁸⁹⁾ and forms the basis of the frontier molecular orbital theory of chemical reactivity⁽⁹⁰⁾. This theory was first applied to the reactivity sequences of 1,3-dipolar cycloadditions by Sustmann^(91,92).

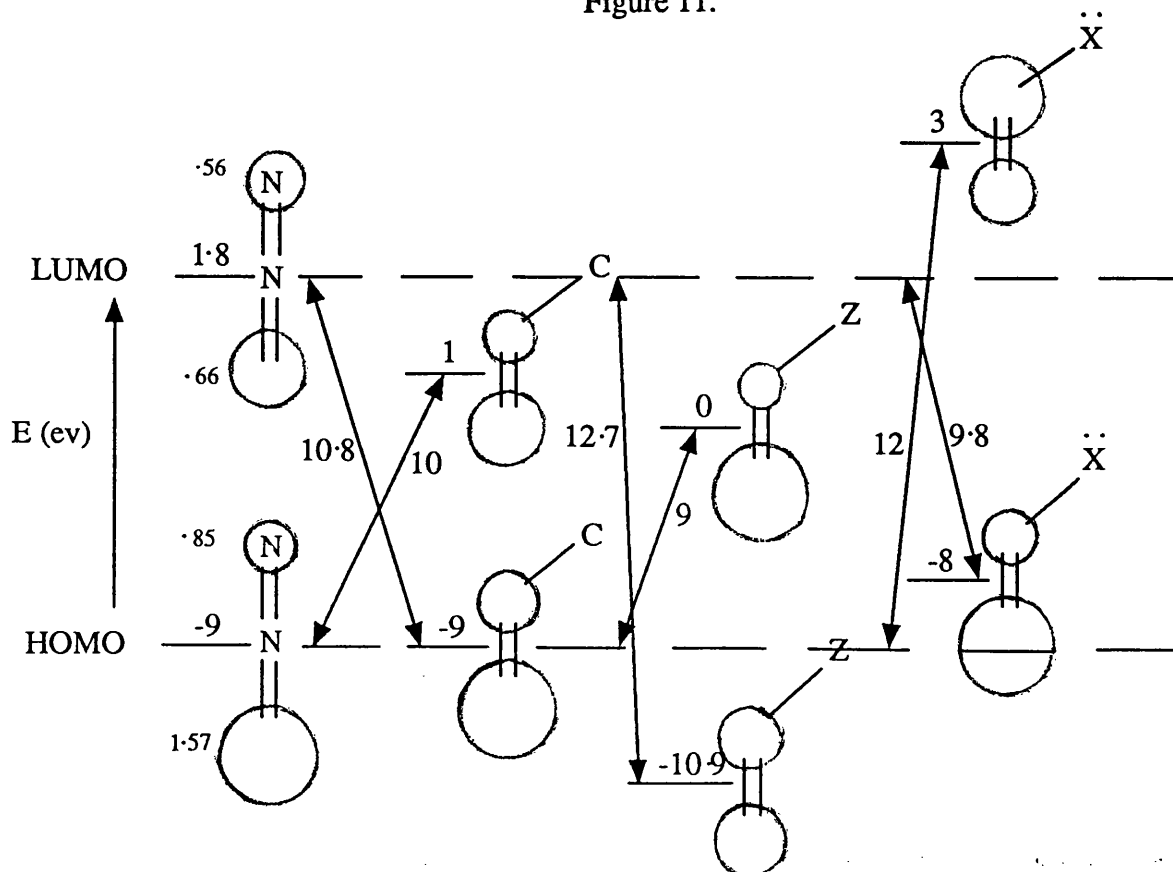
If the smallest energy separation is between the

HOMO of the dipole and the LUMO of the dipolarophile, as will be the case with electron deficient dipolarophiles, then the reaction is termed dipole-HO controlled. If the opposite energy separation is the smallest, then the reaction is termed dipole-LU controlled.

Having discovered which interaction is of primary importance, it is next necessary to look at the coefficients of the relevant orbitals. These and the energies involved in the case of diazomethane and some prominent types of dipolarophiles are shown in figure 11.

Frontier orbitals for diazomethane and dipolarophiles.

Figure 11.



C = conjugating substituent Z = e⁻ withdrawing substituent
X = e⁻ donating substituent

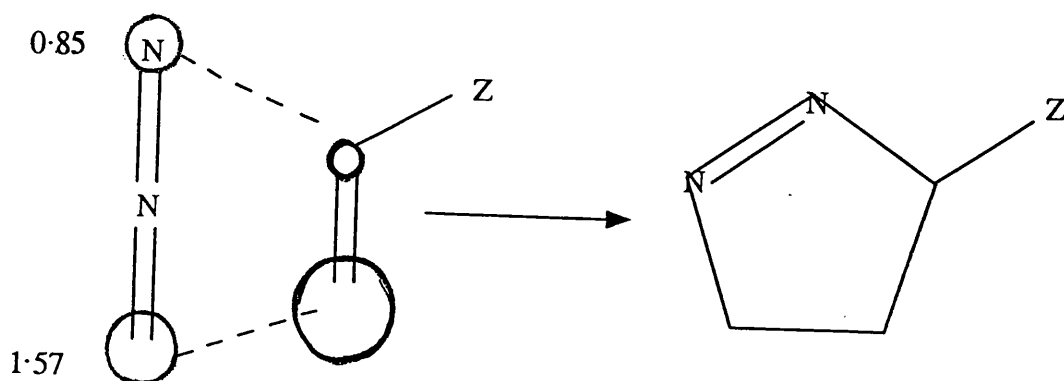
size of sphere is proportional to coefficient size

The favoured regioisomer will be the one formed through the transition state in which atoms with the larger coefficients overlap.

For instance, the reaction of diazomethane with a Z substituted olefin, as shown in figure 12, will be influenced most by the interaction of the HOMO of the dipole and the LUMO of the alkene, since this 9ev gap is smaller than the gap between the HOMO of the alkene and the LUMO of the dipole.

Moreover, the coefficients of the termini indicate that the carbon of the dipole will overlap most effectively with the unsubstituted carbon of the dipolarophile to yield the 3-substituted delta' pyrazoline as opposed to the 4-substituted analogue, as shown in figure 12. It is always the case that for the various coefficients and combinations, the overlap of large with large and small with small is more effective than large-small and small-large.

Figure 12.



size of sphere is proportional to coefficient size

Where the energy separation between the dipole HOMO and the dipolarophile LUMO becomes equivalent to that between the dipole LUMO and the dipolarophile HOMO, the regioselectivity is reduced. The same result is obtained if the orbital coefficients on one of the reactants are similar.

Stereoselectivity in 1,3-dipolar cycloadditions.

As long as the 1,3-dipole and the dipolarophile are configurationally stable, no rotation about the crucial bonds will occur during the concerted formation of the new sigma bonds. Hence retention of configuration should occur.

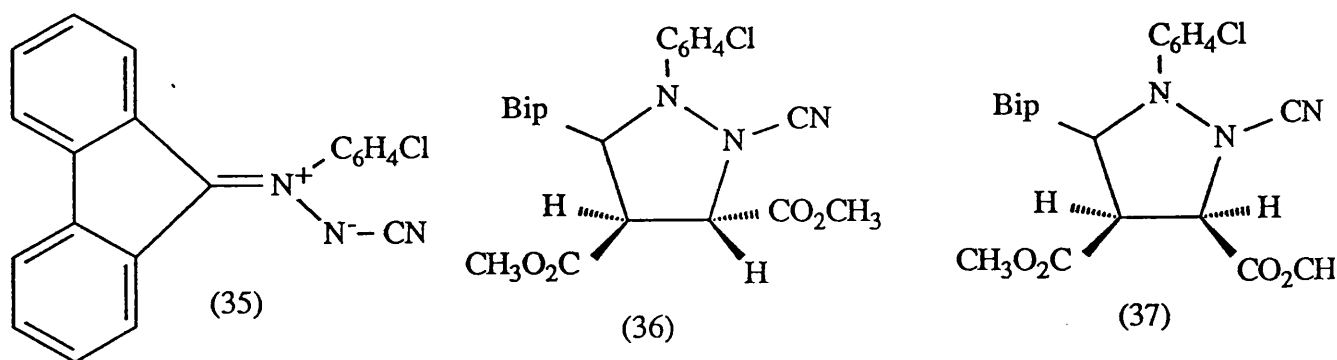
Dipolarophiles with two sp^2 hybridised carbon atoms, such as cis, trans isomeric olefins are necessary to provide information on stereoselectivity.

Of the 1,3-dipoles, only the azomethine ylides possess the necessary terminal sp^2 hybridised carbon atoms needed to test stereoselectivity.

There are numerous examples in the literature of the retention of dipolarophile configuration during 1,3-dipolar cycloadditions(78,79,80,81,93,94,95). Thus, the azomethane imine [35], shown in figure 13, reacts with dimethyl fumarate to give the stereoisomer [36] and with

dimethyl maleate to give the opposite stereoisomer [37](96).

Figure 13



Bip = 2,2',-biphenylene.

The retention of 1,3-dipole configuration in the reaction of azomethine ylides has also been documented(97,98). For example, when dimethyl acetylene dicarboxylate reacts with dimethyl 1-(4-methoxyphenyl) aziridine-trans-2,3-dicarboxylate [38], at 100°C, only the cis-pyrrolidine [39] is obtained. When it is reacted with the cis-aziridine [40], only the trans-pyrrolidine [41] is obtained(99). See figure 14.

Figure 14.

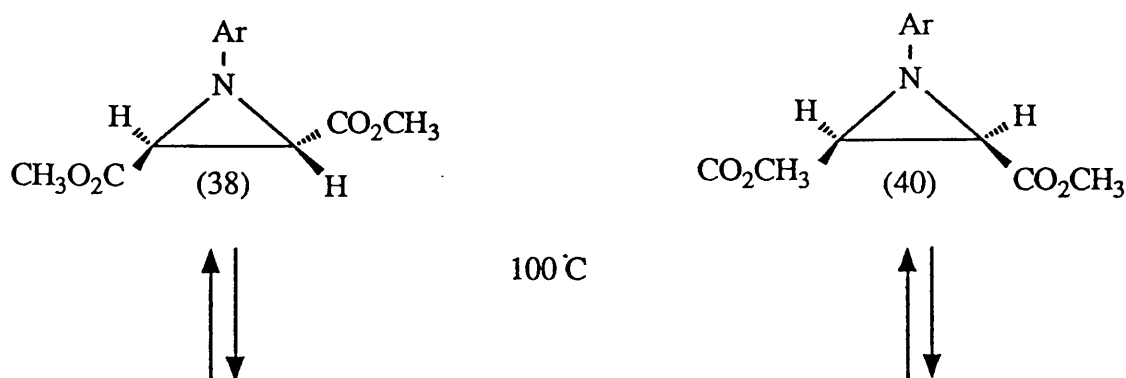
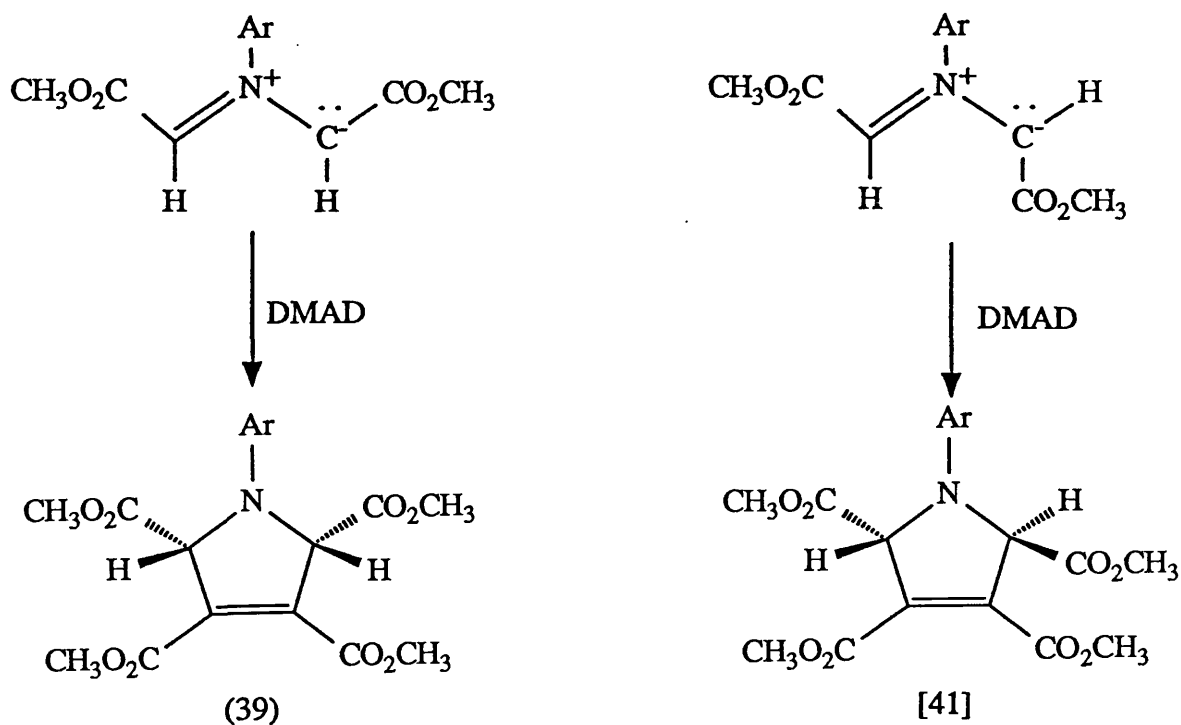


Figure 14 continued.



Azomethine imines.

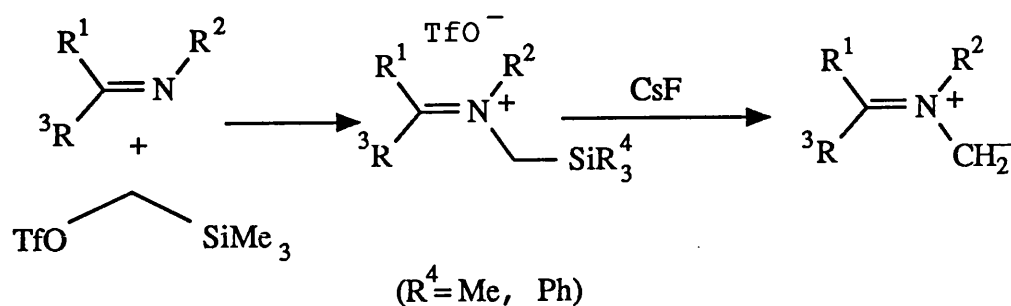
The cycloaddition of this group of 1,3-dipoles with olefinic and acetylenic dipolarophiles produces pyrrolidines, pyrrolines and pyrroles. Azomethine imines are becoming increasingly important in the formation of many natural products^(100,101), in which nitrogen-containing five-membered rings are central components.

Many methods of generation of azomethine ylides exist, which include;

The desilylation of trimethyl or triphenylsilyl compounds

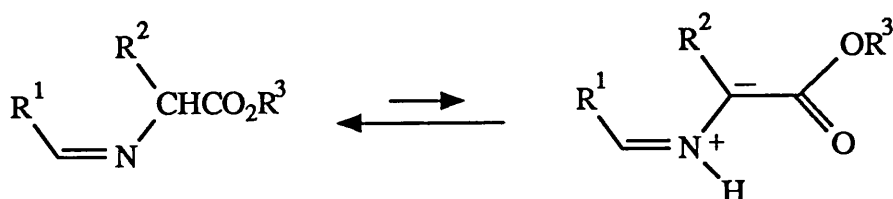
discovered by Vedejs(102,103).

Figure 15.



The thermal tautomerization of imines(104,105).

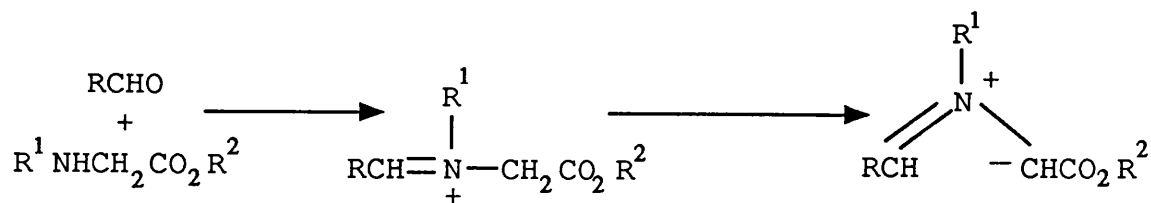
Figure 16.



Thermal or photochemical opening of aziridines, as mentioned previously(99).

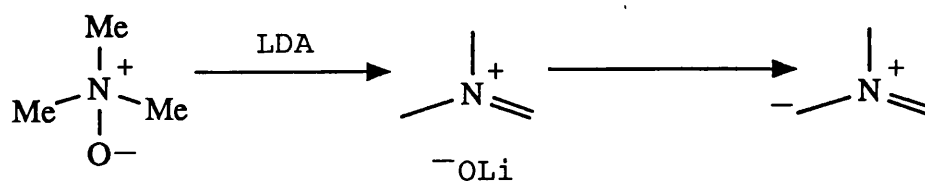
The condensation of 2-amino esters with carbonyl compounds(106).

Figure 17.



The deprotonation of amine N-oxides(107).

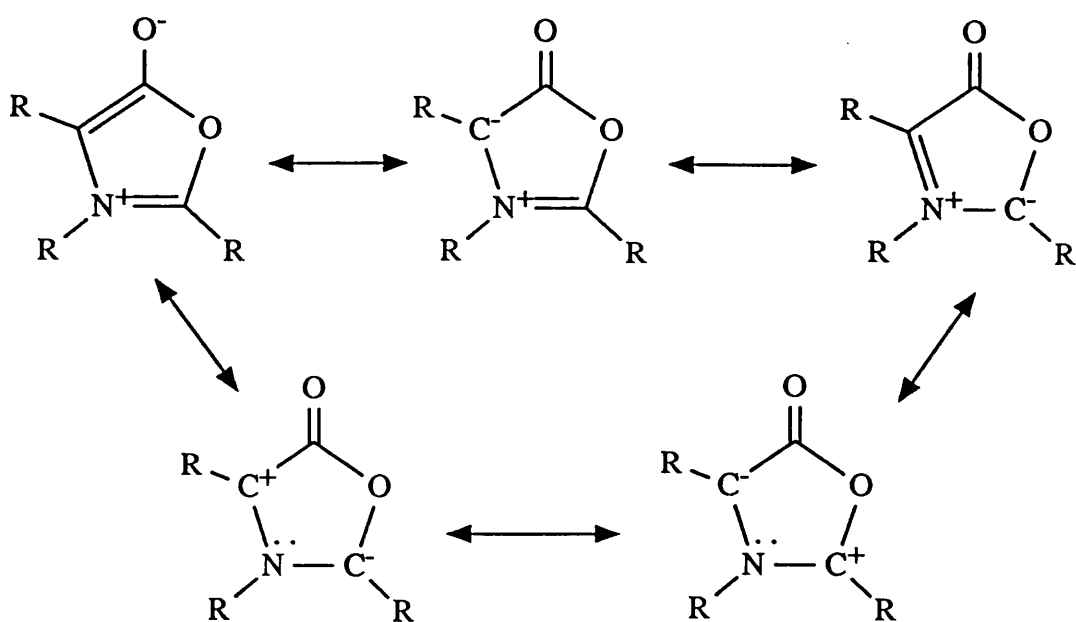
Figure 18.



The generation of mesoionic oxazolones, on which our studies focus.

Mesoionic oxazolones.

Figure 19.

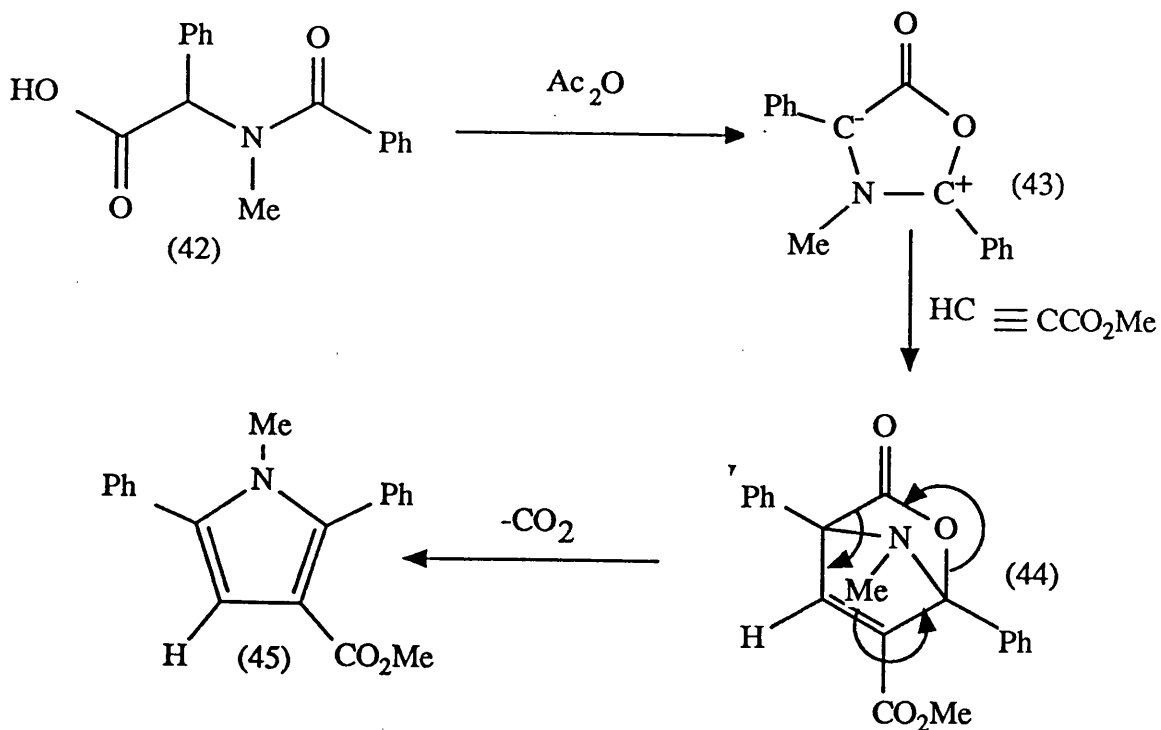


Oxazolones, as shown in figure 19, are the internal anhydrides of N-acylamino acids. Their ability to function as masked azomethine ylides was first recognised by Huisgens group in 1964 in Munich⁽¹⁰⁸⁾, hence the nickname munchnones.

These compounds are very reactive and not easily isolated. In most cases, they are generated from the reaction of acetic anhydride with the N-acylamino acid and are then reacted in situ with the dipolarophile.

Their reactions with alkynes, as shown in figure 20, are a very convenient method of forming pyrroles. For example, methyl propiolate adds exothermically at 0°C to the oxazolone [43], derived from N-benzoyl-N-methylphenylglycine [42]. The initial adduct formed is [44], which rapidly eliminates carbon dioxide to give the aromatized pyrrole [45]⁽¹⁰⁹⁾.

Figure 20.



Discussion and results.

The initial direction of research was towards the synthesis of a range of simplified camptothecins lacking the lactone ring. Since it seems likely that the lactone ring functions as a centre for the acylation of bionucleophiles, the elimination of this unit might reduce the unacceptably high level of toxicity of camptothecin itself.

The proposed reaction scheme is shown in figure 21, illustrating the synthesis of amides⁽¹¹⁰⁾ [48] and their elaboration to tetracycles [54] where x and y are functional groups or ring residues.

Figure 21.

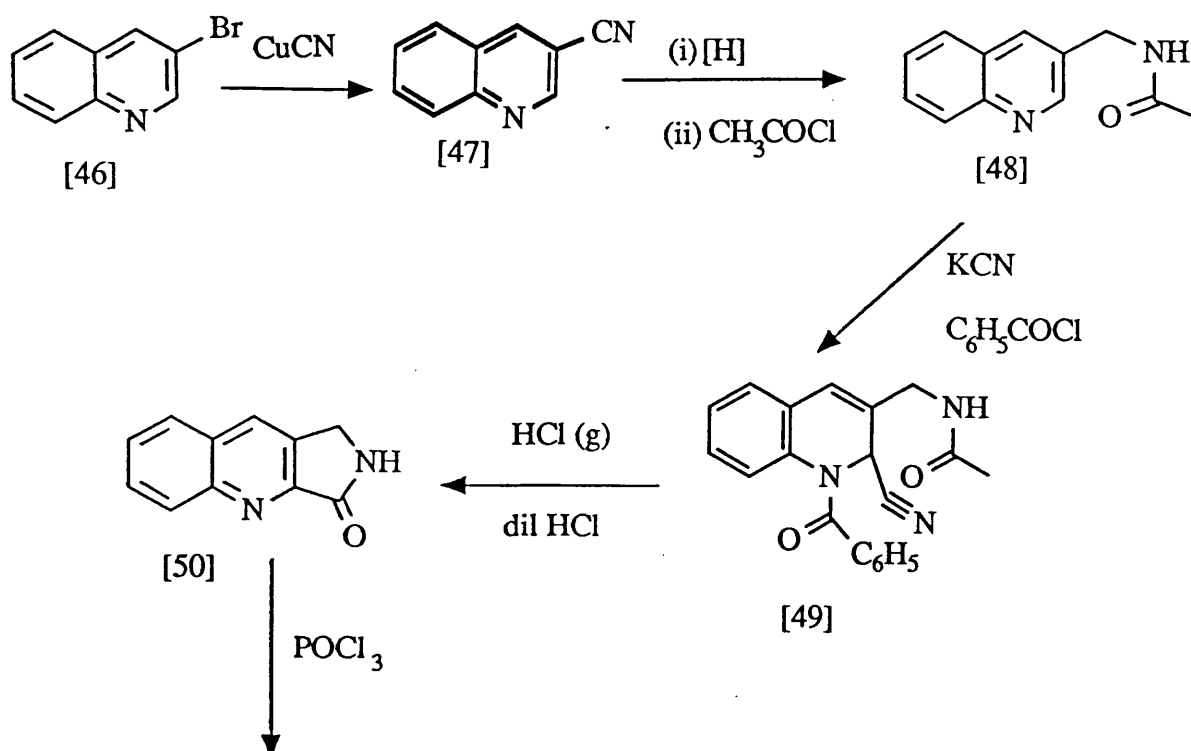
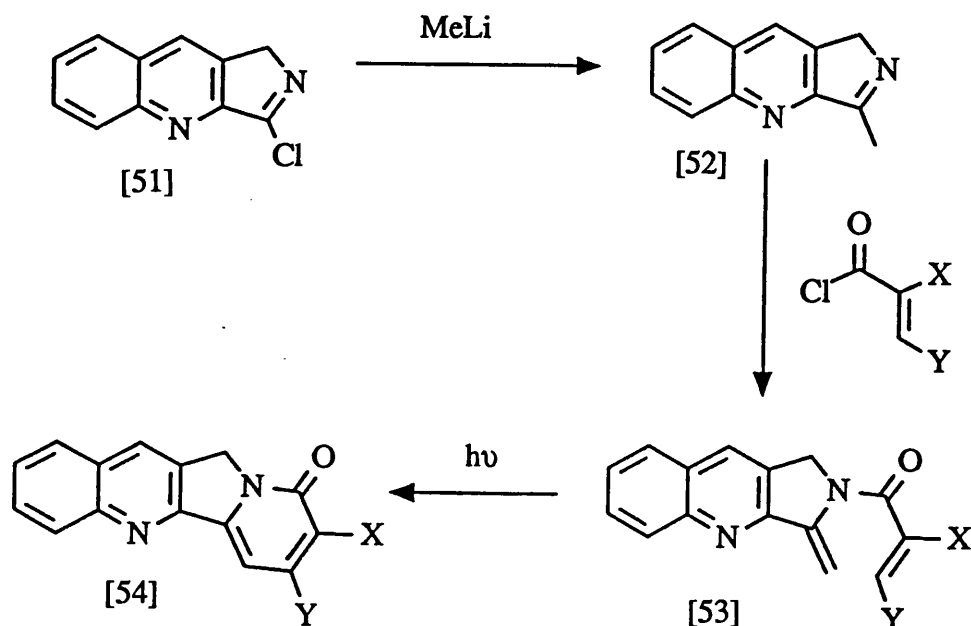


Figure 21 continued.

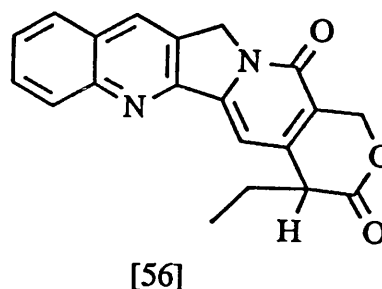
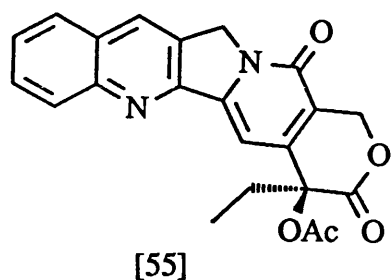


The conversion of 3-bromoquinoline to 3-quinoline carbonitrile [47] was achieved using the Rosenmund Von Braun reaction. The best yield achieved with this method was, however, only 18%.

The next step was the reduction of the nitrile to the amine. A wide range of reducing agents were used to try to effect this transformation. These included lithium aluminium hydride (111, 112), sodium borohydride (113), tetrabutylammonium hydride (114), lithium aluminium hydride and aluminiumtrichloride in combination (115) and catalytic hydrogenation over platinum (IV) oxide (116). No success was achieved with any of these reagents.

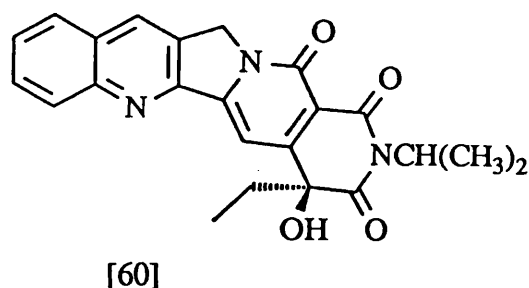
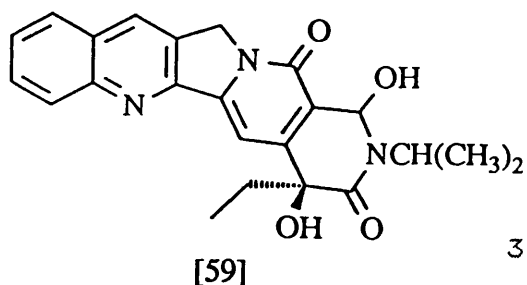
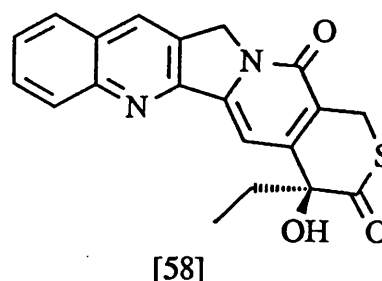
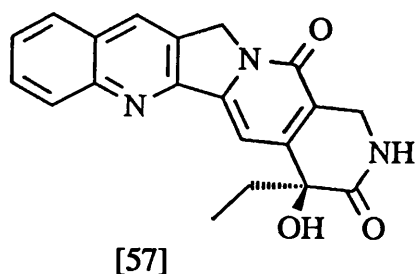
The time we were experiencing the difficulty in achieving this step coincided with the appearance of a

paper published by Hertzberg⁽¹¹⁷⁾. This disclosed that the compounds [55] and [56] were inactive as inhibitors of Topo 1.



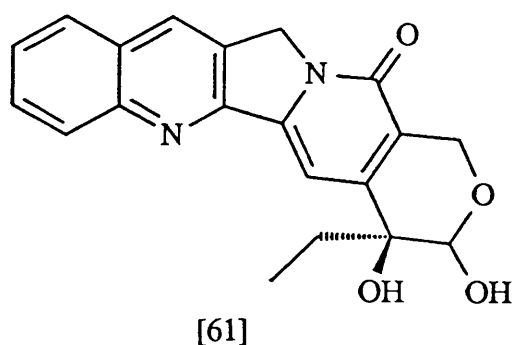
This new evidence⁽¹¹⁸⁾ strongly suggested that the 20-hydroxyl group was essential for anti-tumour activity, a fact due perhaps to the formation of a hydrogen bond between the hydroxy group and the DNA-Topo 1 complex. Alternatively it could be because the hydroxyl group increases the electrophilicity of the lactone carbonyl through intramolecular hydrogen bonding.

Compounds [57],[58],[59] and [60], which retain the hydroxy and carbonyl groups, but which lack the E ring oxygen were also synthesised.



All of these molecules were found not to inhibit Topo 1 and were not cytotoxic. The first of these compounds, [57], differs from camptothecin in that it contains a lactam rather than a lactone ring. In general a lactam ring is more stable to nucleophilic attack than a lactone and the lactam NH is a hydrogen bond donor whilst the lactone ether oxygen is a hydrogen bond acceptor. The thiolactone of [58], whilst more reactive than a lactone, is less able to act as a hydrogen bond acceptor.

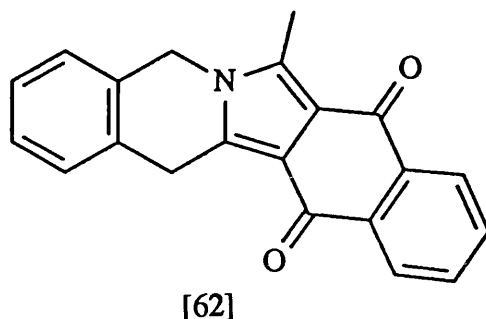
Compound [61] which retains the hydroxyl group and ring oxygen, but which lacks the E ring carbonyl group, was also shown to be pharmacologically inactive.



The strong inference of this work is that the 20-hydroxy group, the carbonyl group and the ring oxygen of the camptothecin E ring are all essential features for Topo 1 inhibition and anti-tumour activity.

These findings led the research to centre instead upon the synthesis of structures related to the pentacyclic quinone 5,13-dihydro-6-methylbenzo[*b*]isoindolo[2,1-

b]isoquinoline-7,12-dione [62] which was first synthesised at Bath in 1981⁽¹¹⁹⁾.



This molecule is also similar to camptothecin in structure and electron density patterns. It has been shown to possess anti-tumour activity and its big advantage over camptothecin lies in its relatively low toxicity.

The synthesis of [62], shown in figure 22, utilised an intermolecular 1,3-dipolar cycloaddition of 1,4-naphthoquinone to the mesoionic oxazolone [63]. This intermediate munchnone was not isolated due to the known high reactivity of the oxazolium-5-olate system ⁽¹²⁰⁾, but was reacted in situ with the naphthoquinone. At the temperature of the reaction carbon dioxide was eliminated from the adduct [64] to generate the pentacyclic product [62] directly in 37% yield.

Figure 22.

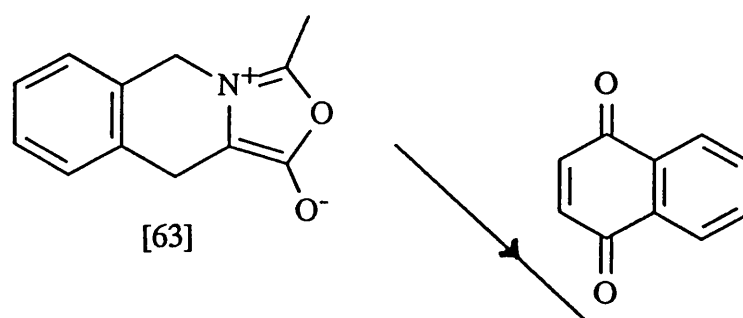
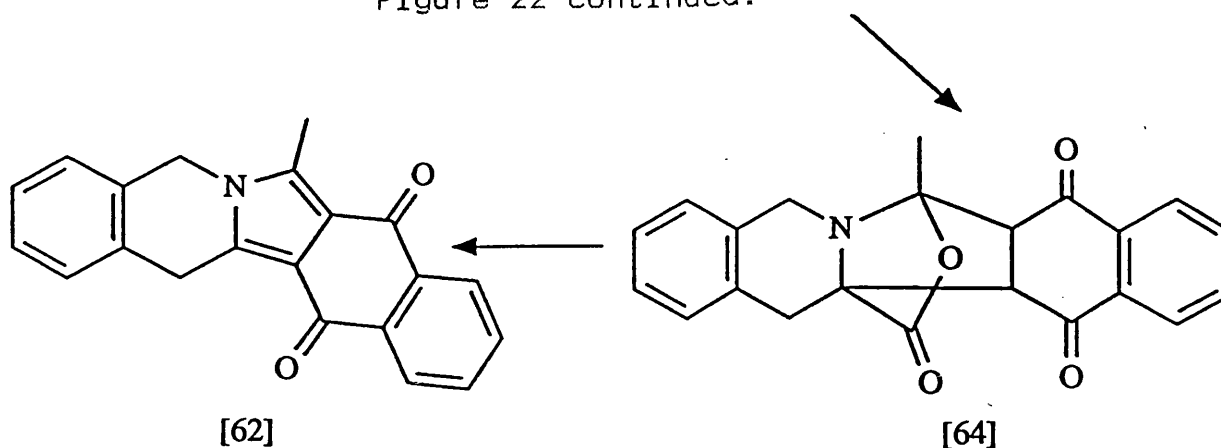
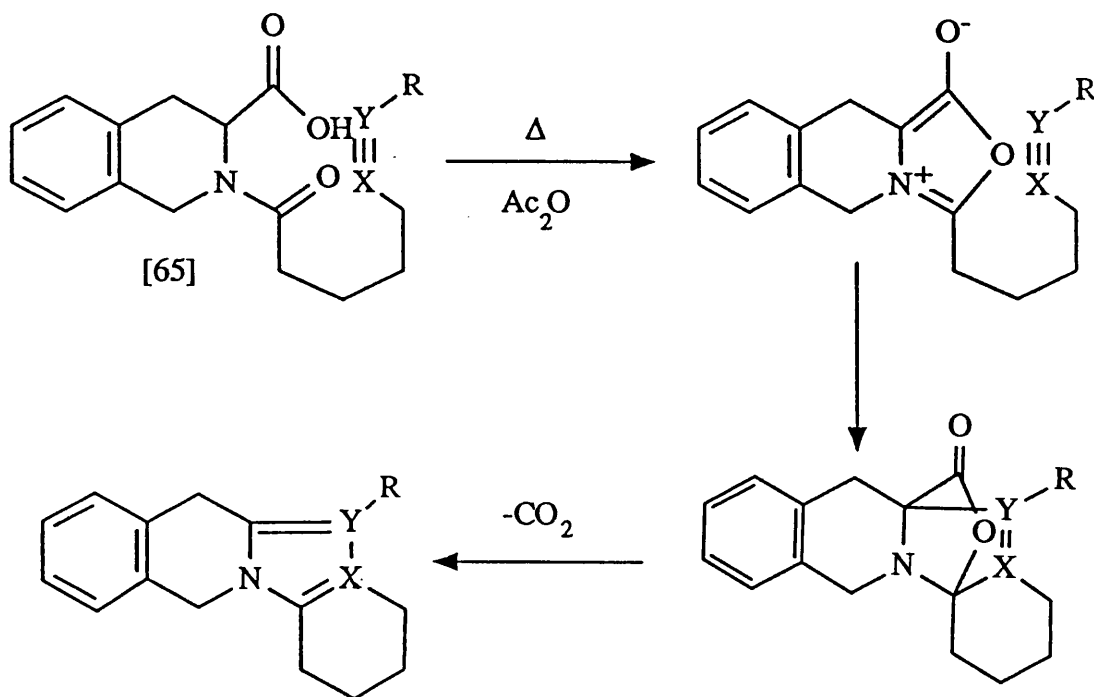


Figure 22 continued.



This type of reaction could provide access to a wide variety of molecules with structures similar to both camptothecin and the pentacyclic [62], especially if an intramolecular cycloaddition approach such as that shown in figure 23 could be implemented.

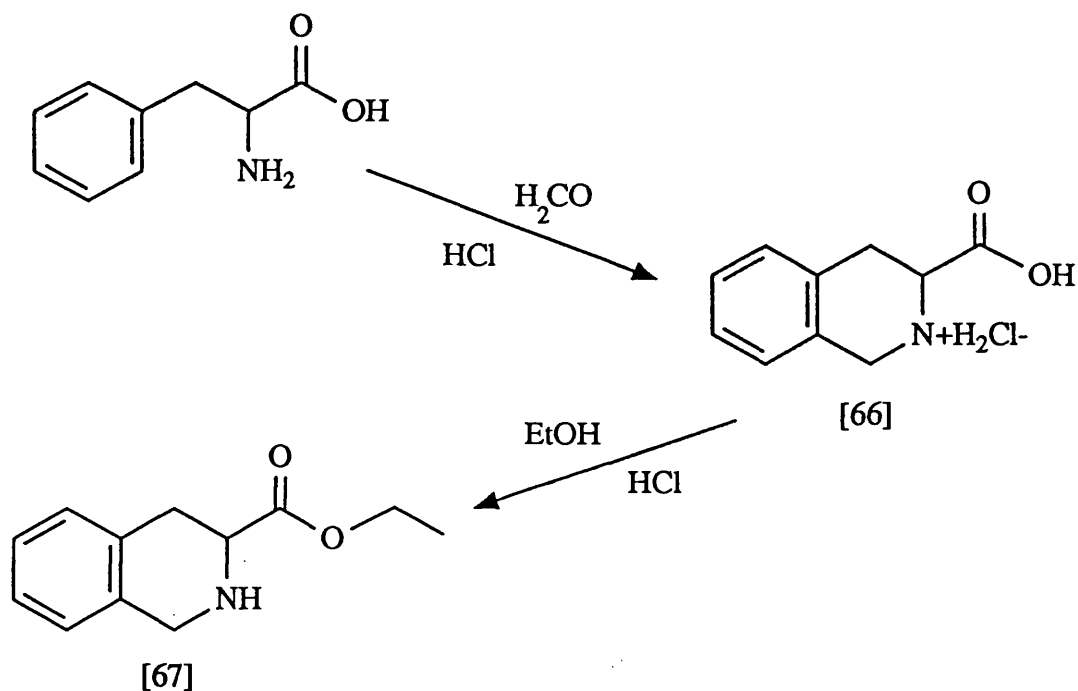
Figure 23.



The basic starting compound for this new line of

research was phenylalanine. This alpha amino acid was converted to 1,2,3,4-tetrahydroisoquinolinium-3-carboxylic acid chloride [66] in good yield by heating at reflux with formaldehyde and concentrated hydrochloric acid, as shown in figure 24. The next step was to convert the acid to an ester so that the subsequent coupling reaction would not be complicated by possible polymerisation. For this step, a suspension of the highly insoluble acid chloride in ethanol was heated whilst dry hydrogen chloride gas was bubbled through the mixture. After basification the esterified product was obtained in very good yield as a pale yellow oil.

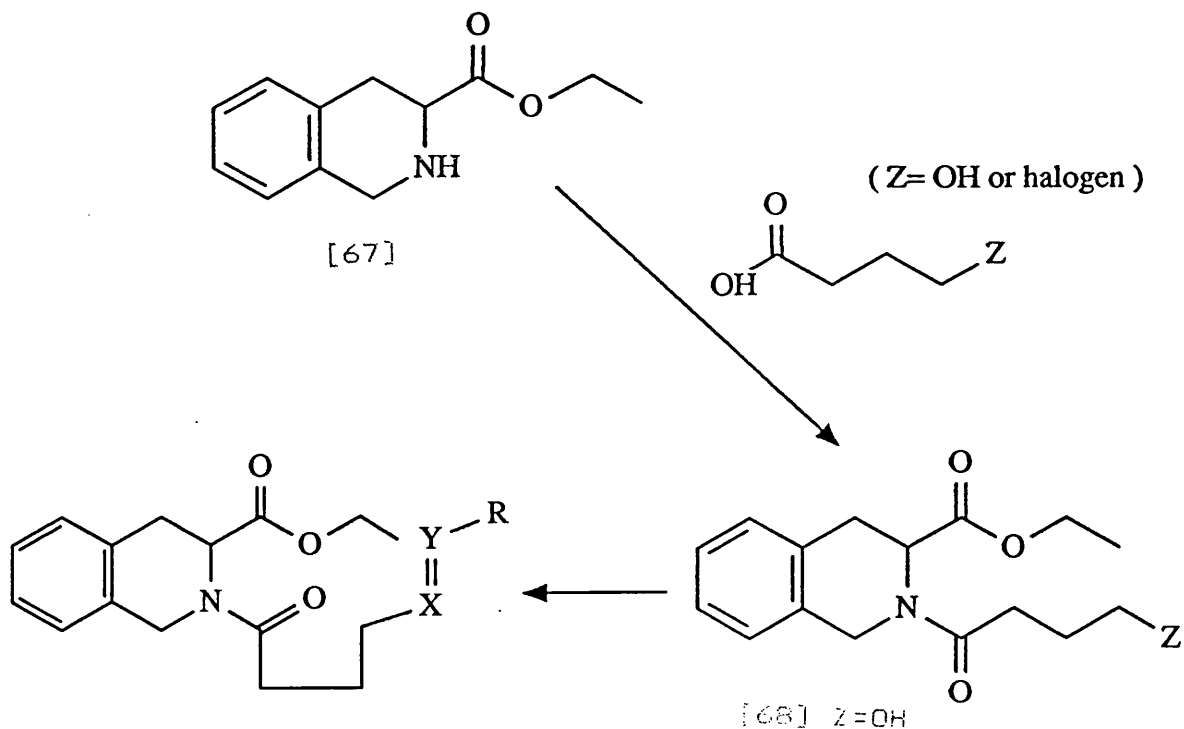
Figure 24.



The next step in the synthesis, as shown in figure 25, was to couple the isoquinoline ester [67] with an

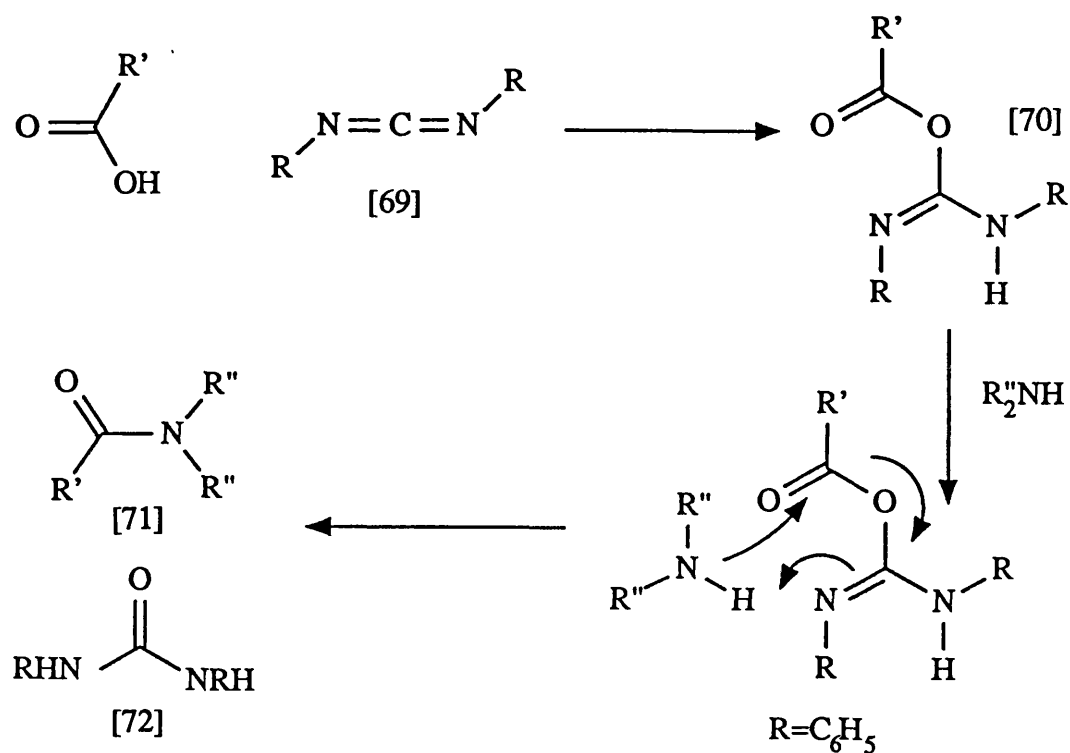
acid bearing a group, z, which could subsequently be converted into a suitable 1,3-dipolarophile.

Figure 25.

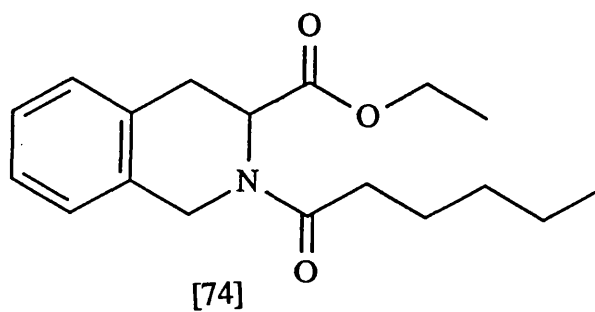
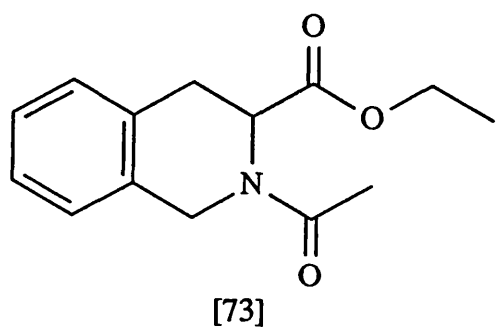


The first coupling reagent used to promote this type of reaction was trimethylaluminium. This was reacted with gamma butyrolactone and [68] was produced but in very poor yield. Next used was 1,3-dicyclohexylcarbodiimide [69] (121, 122). This has been used with much success in the formation of peptides. In the mechanism, shown in figure 26, the hydroxy oxygen of the acid becomes attached to the middle carbon of the carbodiimide. The hydroxy hydrogen leaves and one of the nitrogens of the carbodiimide becomes protonated to form an adduct [70]. Nucleophilic attack by the amine molecule now occurs at the carbamoyl carbonyl group, followed by ultimate loss of the amide [71] and the urea [72].

Figure 26.



Model reactions with acetic acid and hexanoic acid produced the respective amides [73] and [74] in reasonable yields, although the products were always highly contaminated by dicyclohexyl urea which proved very difficult to remove.

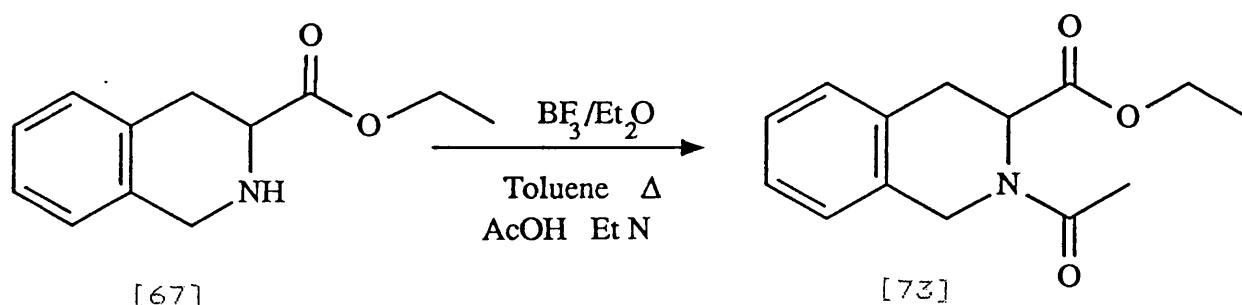


For this reason it was decided to explore other acylation procedures. One of the reagents used was boron

trifluoride etherate (123). This was first widely used in the esterification of carboxylic acids with lower alkyl alcohols, due to its Lewis acid and dehydrating character and we speculated that it might be effective in N-acylating the isoquinoline [67].

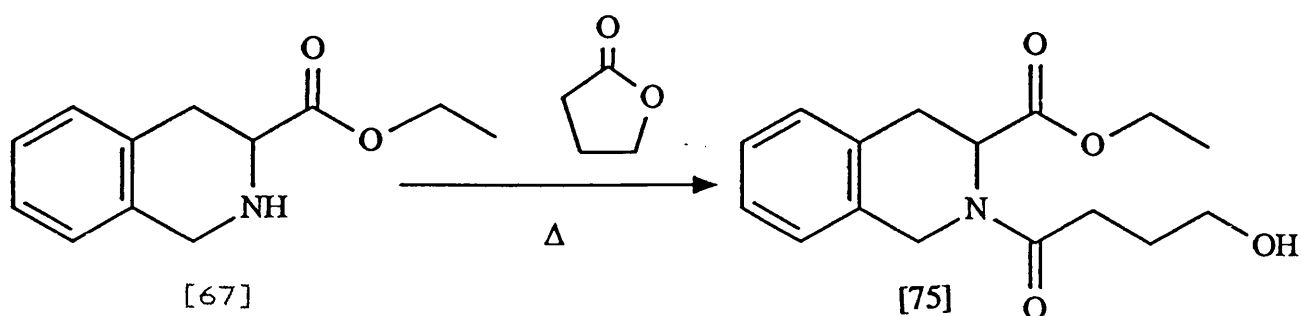
Thus this substrate, acetic acid, triethylamine and boron trifluoride etherate were refluxed with toluene in a Soxhlet apparatus for periods of up to 48h. Although the acetamide product was formed we were unable to achieve greater than a 10% yield.

Figure 27.



The next reaction tried was the direct N-acylation of the isoquinoline ester [67] by heating it with butyrolactone. This, we thought, would give the alcohol [75] as shown in figure 28, which has functionality in the side chain suitable for further elaboration to a dipolarophile. The main product isolated from this reaction however was not [75], but a tan coloured solid with a molecular ion peak of m/z 318 in the mass spectrum. Compound [75] requires a molecular ion peak of m/z 291.

Figure 28.

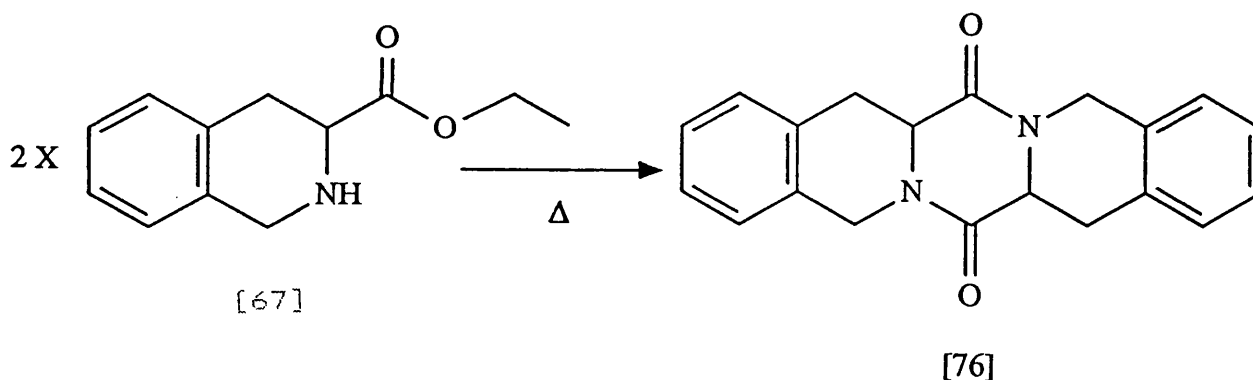


No hydroxyl group absorption was observed in the infrared spectrum and there was no evidence for the presence of an ester group. The ^1H NMR spectrum provided the real clue as to the identity of the product. The spectrum showed no resonances due to aliphatic methyl or methylene protons, which indicated that the ethyl group was no longer present. A ^1H double doublet at 3.02 ppm ($J = 16.0$ Hz, 11.9 Hz) was associated with a similar set of signals at 3.46 ppm ($J = 16.0$ Hz, 3.8 Hz) and again with another set of signals at 4.30 ppm ($J = 11.9$ Hz, 3.8 Hz). The large spin-spin coupling of 16 Hz suggested that the signals at 3.02 and 3.46 ppm are the resonances of a geminal pair of protons with individual 3J couplings to a third proton at 4.60 ppm. Further downfield were two additional ^1H doublets at 4.36 ppm and 5.40 ppm. These exhibited a common coupling constant of $J = 17.7$ Hz and were thus assigned to another pair of geminal protons. The low field protons of these signals are similar in chemical shift to the C-1 protons of the starting isoquinoline ester. A multiplet centred at 7.24 ppm accounted

for another four protons.

All of this information taken together, strongly suggested that the isoquinoline group was still present. The infrared spectrum showed a strong absorption at 1625 cm^{-1} , indicative of an amide carbonyl group, and this, together with a band at 3250 cm^{-1} suggested a lactam. This, coupled with the molecular ion peak of m/z 318 in the mass spectrum led us to conclude that the compound was in fact the diketopiperazine [76], formed from the condensation of two molecules of the isoquinoline ester, shown in figure 29. An accurate mass determination confirmed this conclusion.

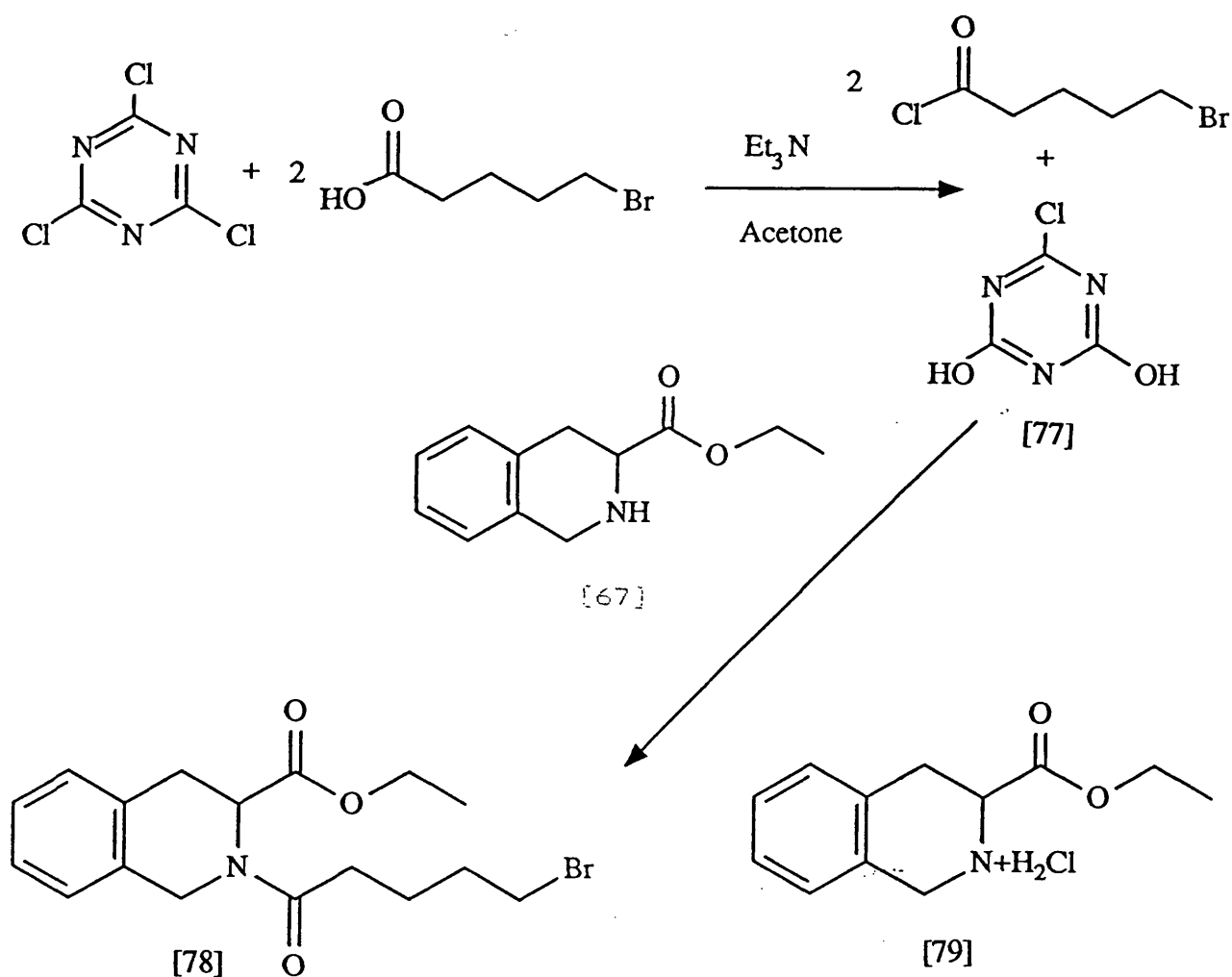
Figure 29.



With this problem in mind we next used cyanuric chloride as the coupling agent. This reagent has been used in a wide variety of reactions including the transformation of alcohols to chlorides⁽¹²⁴⁾, alcohols to iodides (in the presence of sodium iodide)⁽¹²⁵⁾, and oximes to nitriles⁽¹²⁶⁾. It can also be used to convert

carboxylic acids to acid chlorides, and these can be reacted in situ with amines to produce amides. In a paper by Venkataramam a wide variety of acids including acetic, oxalic, malonic, succinic, cinnamic and benzoic acid were converted to anilides in very good yields⁽¹²⁷⁾.

Figure 30.



Hence a solution of 5-bromopentanoic acid, cyanuric chloride and triethylamine in acetone was stirred at 30°C for 3h. As shown in figure 30. The isoquinoline ester [67] was then added and after a further 2h the isoquinoline amide [78] was isolated. The insoluble chlorodihy

droxytriazine [77] could be easily removed by filtration.

The presence of triethylamine in this reaction is necessary to ensure that the amino substrate is deprotonated. However in our reaction we noted that the isoquinolinium chloride [79] was a by product. By adding sodium bicarbonate to the reaction mixture the formation of this salt was repressed and the yield was improved to 82%.

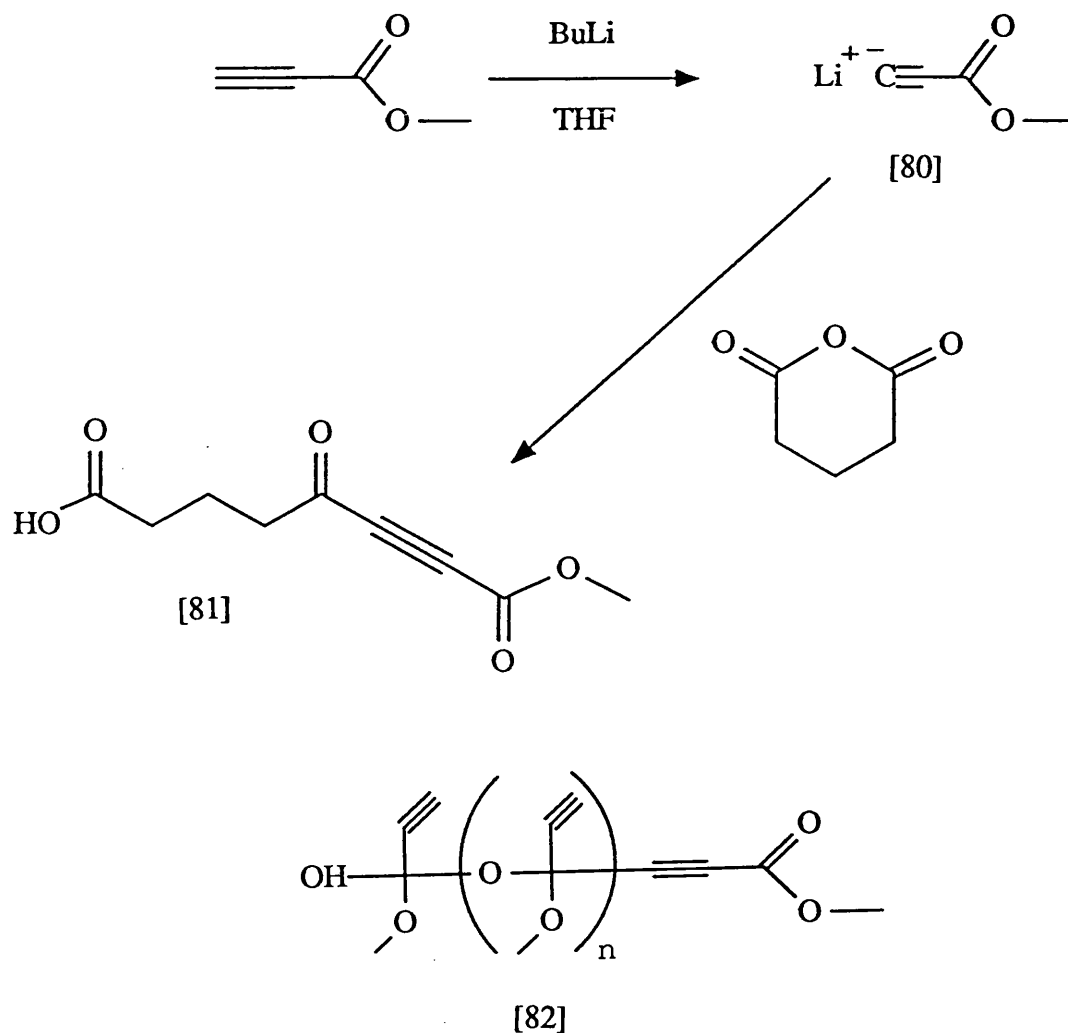
Rather than having a purely linear approach to the formation of the isoquinoline amide [65], a number of reactions were performed to attach the dipolarophile unit to the acid prior to its attachment to the isoquinoline ester.

In the first of these reactions we attempted to form the alkynyl acid [81] as depicted in figure 31. Butyl lithium was added to a solution of methyl propiolate in THF at -78°C to form the propiolate anion [80]⁽¹²⁸⁾. The mixture was stirred for 1h and then a solution of glutaric anhydride in THF was added. The solution was kept at -78°C for a further 2h then allowed to warm to room temperature before quenching with water.

A complex product mixture resulted, which was shown by mass spectrometry to contain high molecular weight material. This could be due to the anion [80] reacting with the carbonyl groups of other propiolate anions and

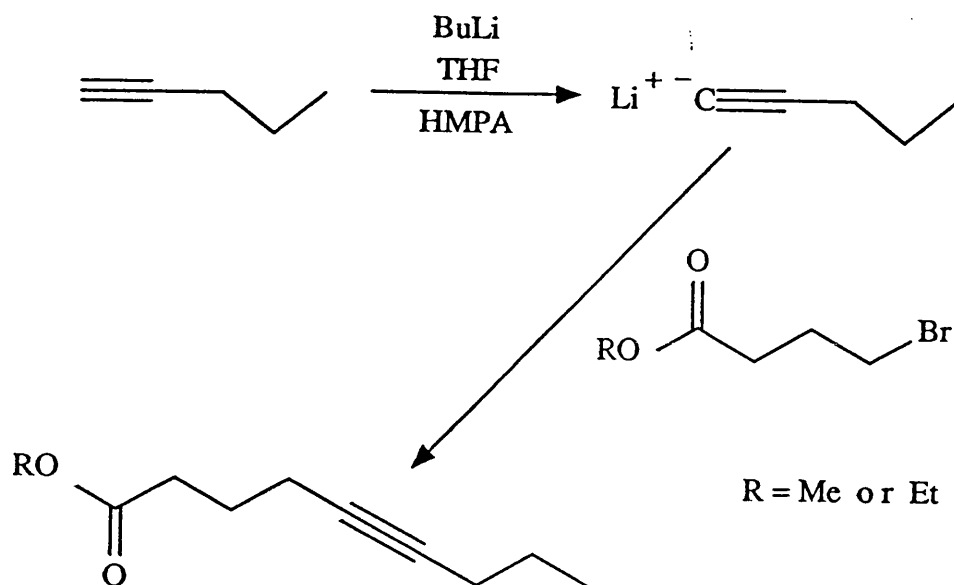
thus forming an oligomer of the type [82].

Figure 31.



To circumvent this problem it was decided instead to use various 4-bromobutanoic esters. Alkylation of 1-pentyne would then form an alkynyl ester, as shown in figure 32. This time, hexamethyl phosphoramide (HMPA) was added to the reaction mixture to more readily solvate the anions and to reduce the chance of lithium aggregates forming.

Figure 32.



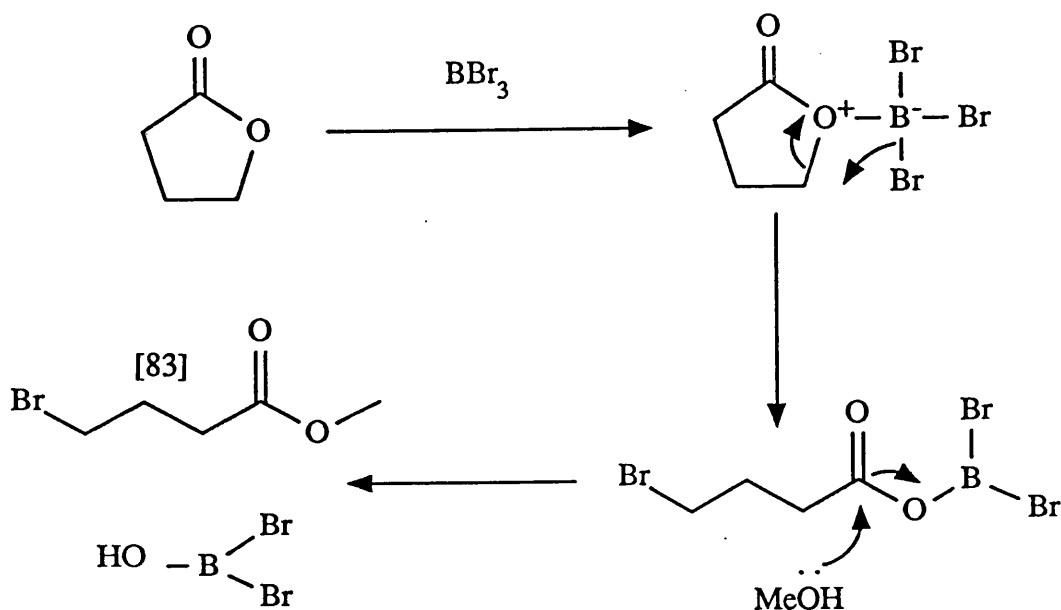
Again, complex product mixtures were obtained and spectral evidence suggested that the pentyne anion was attacking at the carbonyl group of the ester rather than displacing the halogen atom as bromide ion.

Two methods were employed to synthesize the bromoesters required for these experiments. In the first, boron tribromide was used. This reagent has successfully been used to convert 4,5,6 and 7 membered lactones to their corresponding bromoacids and bromoesters and in combination with sodium iodide to form the iodoacids and esters (131).

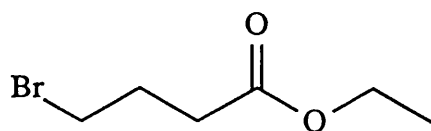
Hence, gamma butyrolactone was added to a solution of boron tribromide in dichloromethane at room temperature

under an atmosphere of nitrogen. After 14h the reaction mixture was quenched with methanol. This yielded the methyl bromoester [83] although only in 53% yield. Shown in figure 33.

Figure 33.



In the second method^(132,133,134), the esterification was performed by passing dry hydrogen bromide gas through a solution of the butyrolactone in ethanol at 0°C . The solution was then stirred at room temperature for 2h then quenched with ice. This yielded the ethyl bromoester [84] in a much better yield of 83%.



[84]

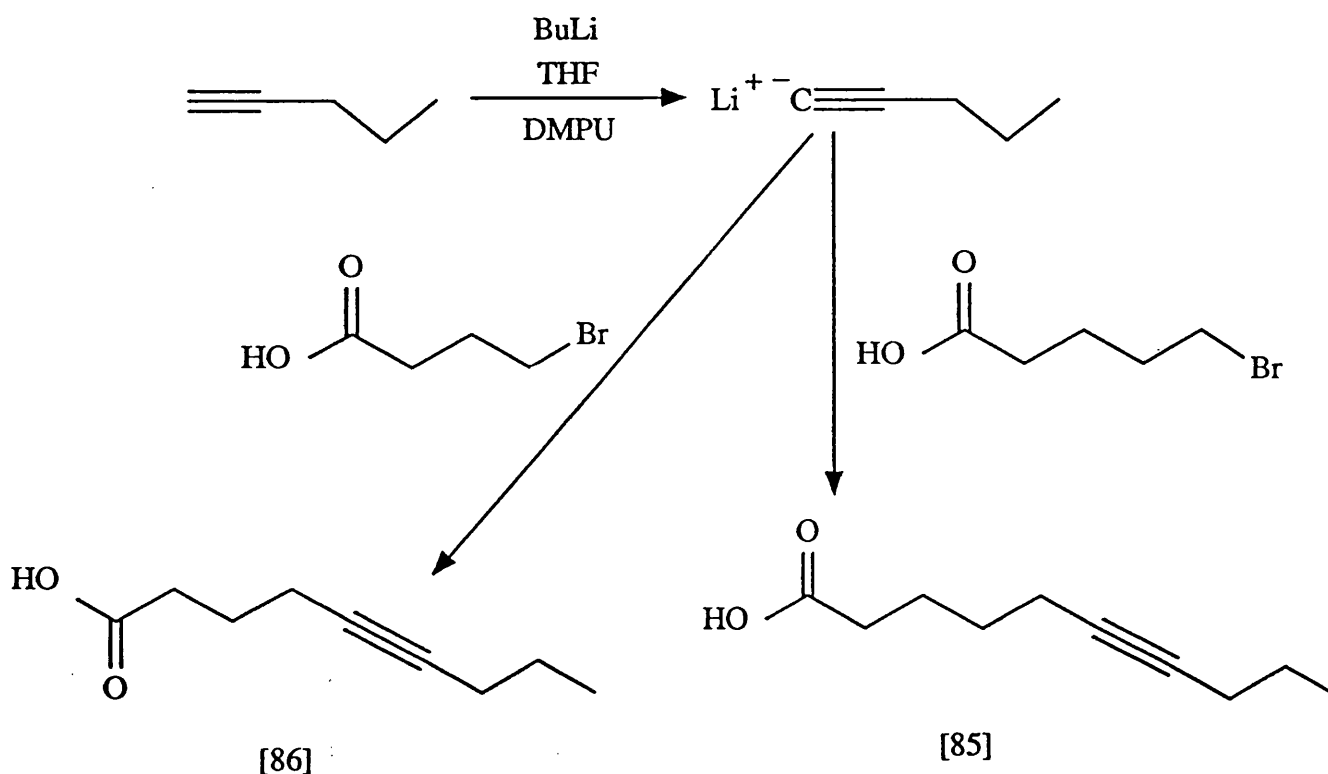
Due to the poor results obtained in the alkylation of these esters it was decided to use instead the free

acids. Now, attack at the carbonyl group is unlikely. 5-bromovaleric acid was selected as the alkylating agent.

1,3-Dimethyl 3,4,5,6-tetrahydro 2[1H] pyrimidinone (DMPU)(135,136) was used as a solvating agent in place of HMPA. The advantage of this reagent is that, whilst it possesses good cation solvating properties, it lacks the carcinogenic properties associated with HMPA.

Hence BuLi was added to a solution of 1-pentyne in THF and DMPU at -78°C under nitrogen. After 1h at this temperature 5-bromopentanoic acid was added and the solution was then allowed to warm to room temperature prior to the addition of water. Unfortunately, mainly starting materials were obtained upon work up. This was disappointing and we could not explain this failure.

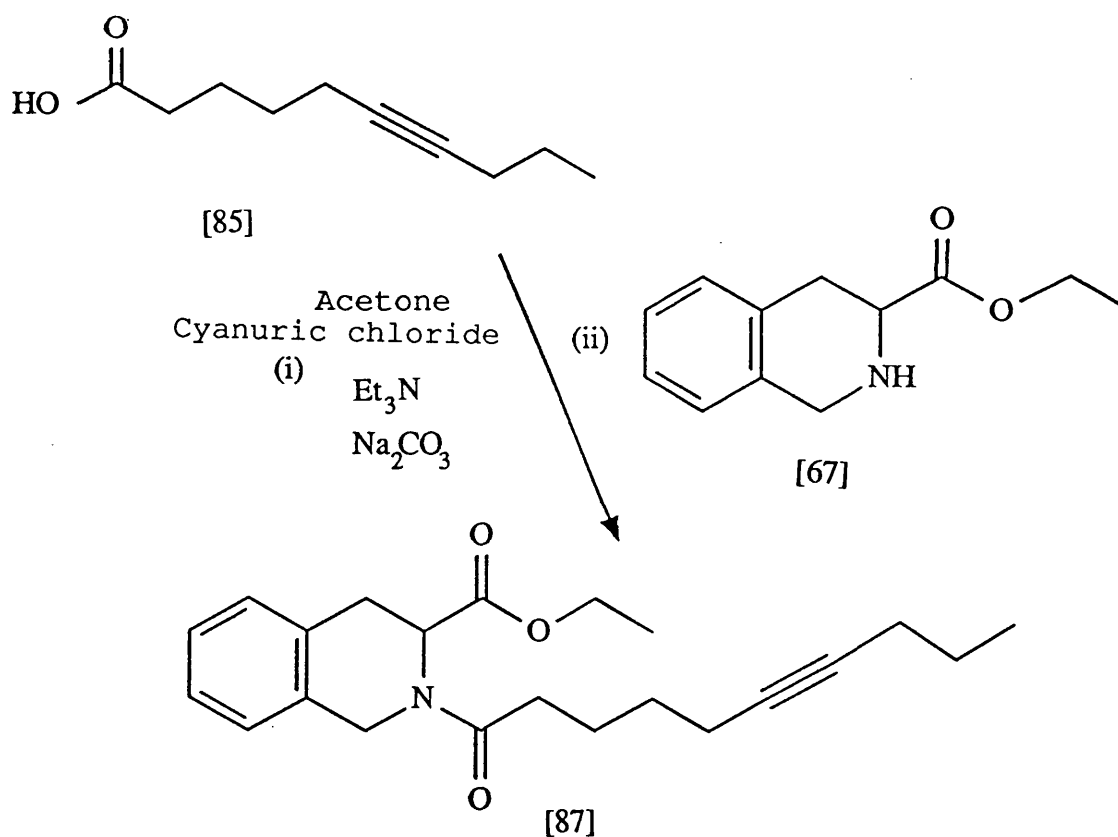
Figure 34.



The experiment was repeated and after warming to room temperature this time, the reaction mixture was immersed in a sonic bath for 2h before work up. This furnished the desired 6-decynoic acid [85] in 35% yield. The corresponding 5-nonynoic acid [86] was obtained in a similar fashion in 31% yield. Shown in figure 34 above.

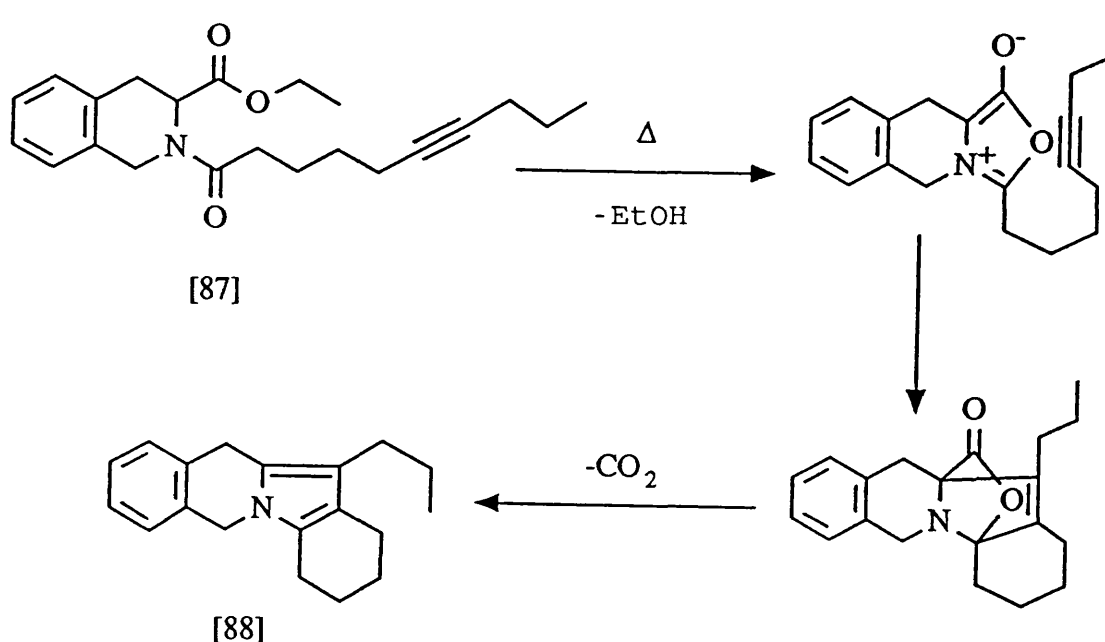
We were then able to proceed to the next stage, as shown in figure 35, where the alkynyl acid [85] was dissolved in acetone and triethylamine. Cyanuric chloride was then introduced and after warming the reaction mixture to 40°C the isoquinoline [67] and sodium carbonate were added. After 3h the isoquinoline amide [87] could be isolated in 75% yield.

Figure 35.



Attempts were next made to cyclise the alkynyl isoquinoline as depicted in figure 36. Because attempts to purify [87] by distillation had resulted in decomposition of the molecule, it was aimed to keep the temperature of the reaction as low as possible. Heating [87] in acetic anhydride at 80°C for 7h produced none of the cyclised material [88]. Increasing the temperature to 135°C and refluxing for 14h resulted in enhanced decomposition and no cyclised product.

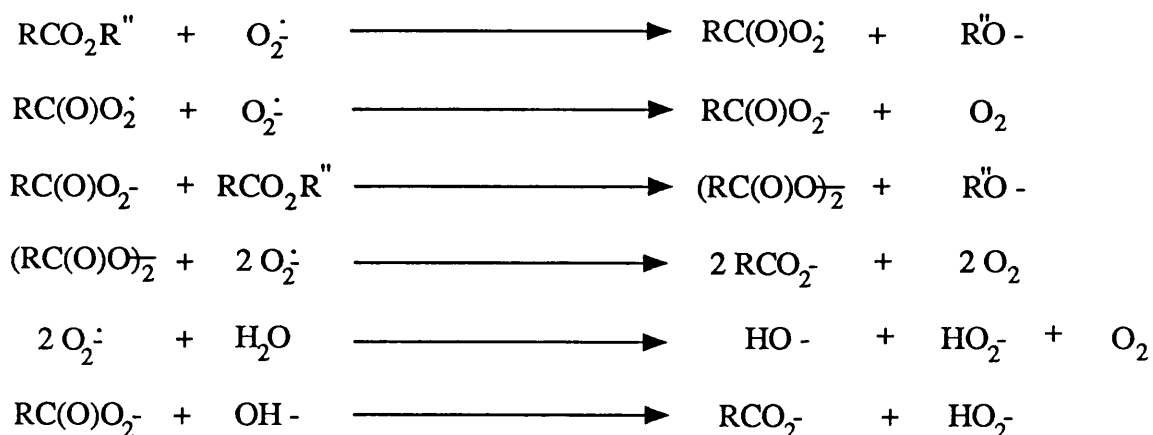
Figure 36.



It was decided that in order to enhance the possibility of cyclisation, the ester should be saponified to the acid. This would enable a better leaving group, an anhydride, to be formed at this position when the substrate was heated with acetic anhydride.

One method for cleaving an ester without hydrolysing an amide involves the use of potassium superoxide⁽¹³⁷⁾ in benzene, with 18-crown 6-ether to enhance the solubility of the superoxide. The mechanism of this reaction, as shown in figure 37, involves nucleophilic attack by the superoxide anion at the carbonyl carbon of the ester followed by electron exchange, the liberation of oxygen and the formation of the anion of the corresponding peracid. This sequence, unique to esters, then continues as a chain process affording the monocarboxylate anion as one product.

Figure 37



This reaction, when applied to our substrate, worked well and the acid [89] was produced in 77% yield after stirring the solution of [87] for 14h with potassium superoxide at room temperature. De-esterification was later also achieved by simply reacting the isoquinoline [87] with sodium hydroxide in a solution of THF and water at room temperature for 12h. The yield in this case was

marginally better at 79%. Shown in figure 38.

Figure 38.

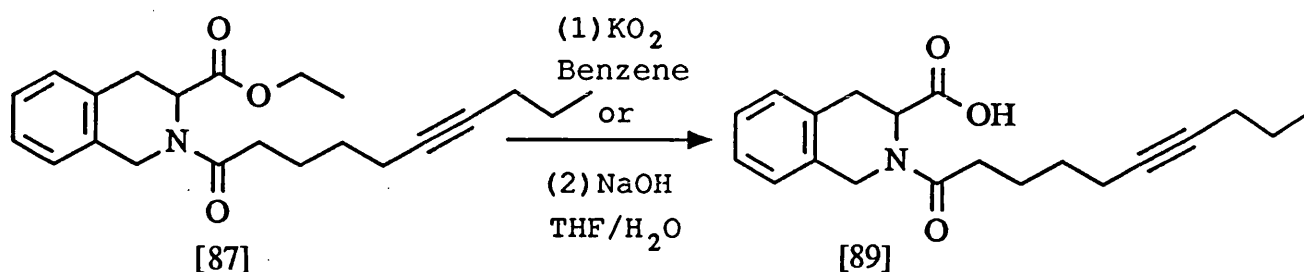
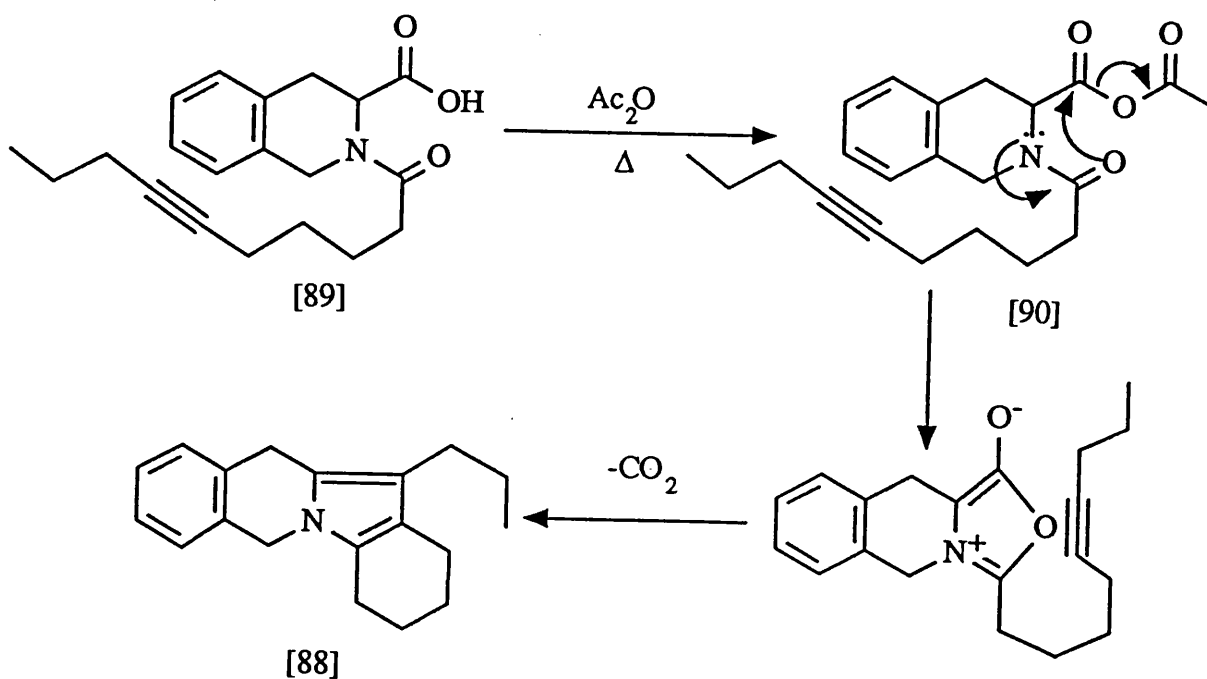


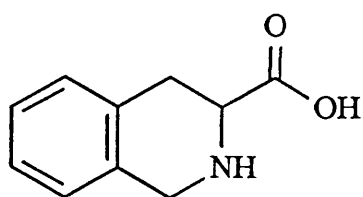
Figure 39.



The acid [89] was then heated in acetic anhydride for 14h at 60°C . It was hoped that the acid group at position 3 would react with acetic anhydride to form the mixed anhydride [90]. This unit would function as a much better leaving group than the ethoxy group of the related

ester and enhance the formation of the mesoionic compound and hence the cyclised product. Shown in figure 39 above.

No cyclised product was obtained at 60°C, nor even could any be detected after heating for 3 days at 135°C. This was another disappointment, and in order to gain insight into the nature of the dipolarophiles which will participate in these types of intramolecular cycloadditions it was decided to investigate a number of different intermolecular cycloadditions using 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid [91] as the latent mesoionic compound. The acid [91] was produced by dissolving the isoquinolinium chloride [66] in the minimum volume of hot ethanol and water (2:1) and then carefully neutralising with ammonium hydroxide until the solution was just acid to congo red. The free amino-acid crystallised as colourless plates upon cooling.



[91]

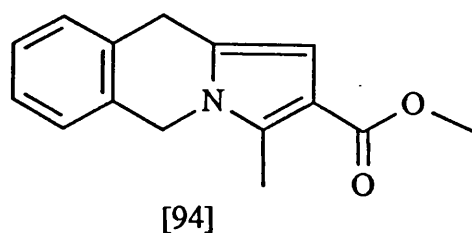
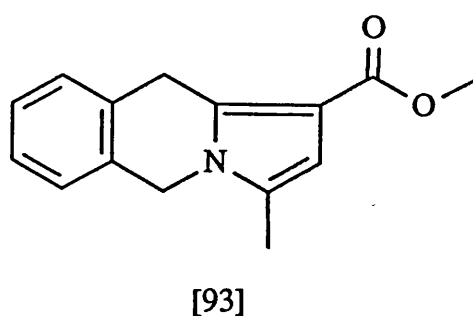
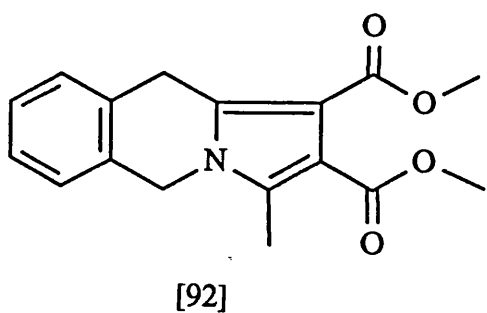
Work by Huisgen^(138,139) and Hershenson⁽¹⁴⁰⁾ suggested that the most successful dipolarophiles are those containing electron withdrawing substituents such as methoxycarbonyl groups. Also, acetylenic dipolarophiles

were more effective than the corresponding olefinic dipolarophiles.

This led us to investigate dimethylacetylene dicarboxylate (DMAD) and methyl propiolate as our primary dipolarophiles.

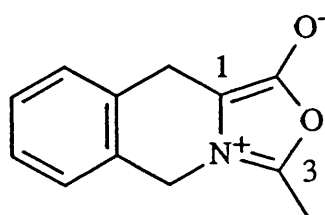
Hence [91] was dissolved in a solution of acetic anhydride and DMAD and heated at 80°C until no more carbon dioxide was evolved. After work up the corresponding dihydropyrroloisoquinoline [92] was obtained in 63% yield.

A similar reaction with methyl propiolate yielded both the regioisomers [93] and [94] in an approximately 1:1 ratio, after the reaction mixture was heated at 100°C for 2h.



Such regioisomerism is not unknown and there are several reports of similar reactions in the literature^(138,140,141).

One explanation for our result is that the orbital coefficients at C-1 and C-3 in the intermediate munchnone [95], shown below, are similar or alternatively this could indicate that the energy gap between the HOMO of the dipole and the LUMO of the dipolarophile is of a similar value to that between the dipole LUMO and the dipolarophile HOMO.

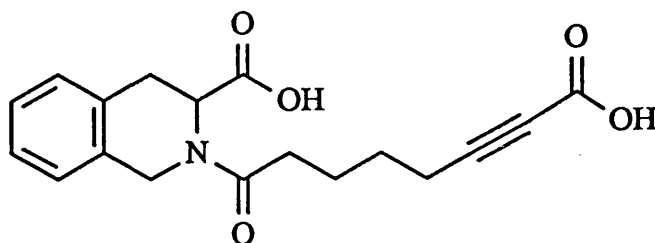


[95]

In the reactions of the isoquinoline acid [91] with the olefinic dipolarophiles methyl methacrylate, dimethyl fumarate and dimethyl maleate, complex, inseparable mixtures of products were obtained, but no evidence was obtained for the formation of any addition products. Similar problems were also encountered by Hershenson⁽¹⁴⁰⁾ with these types of dipolarophiles. He too obtained complex, multi-component product mixtures.

From the encouraging results obtained with DMAD and

methyl propiolate it was decided to synthesise the following molecule, [96], as a candidate for the intramolecular cyclisation reaction.



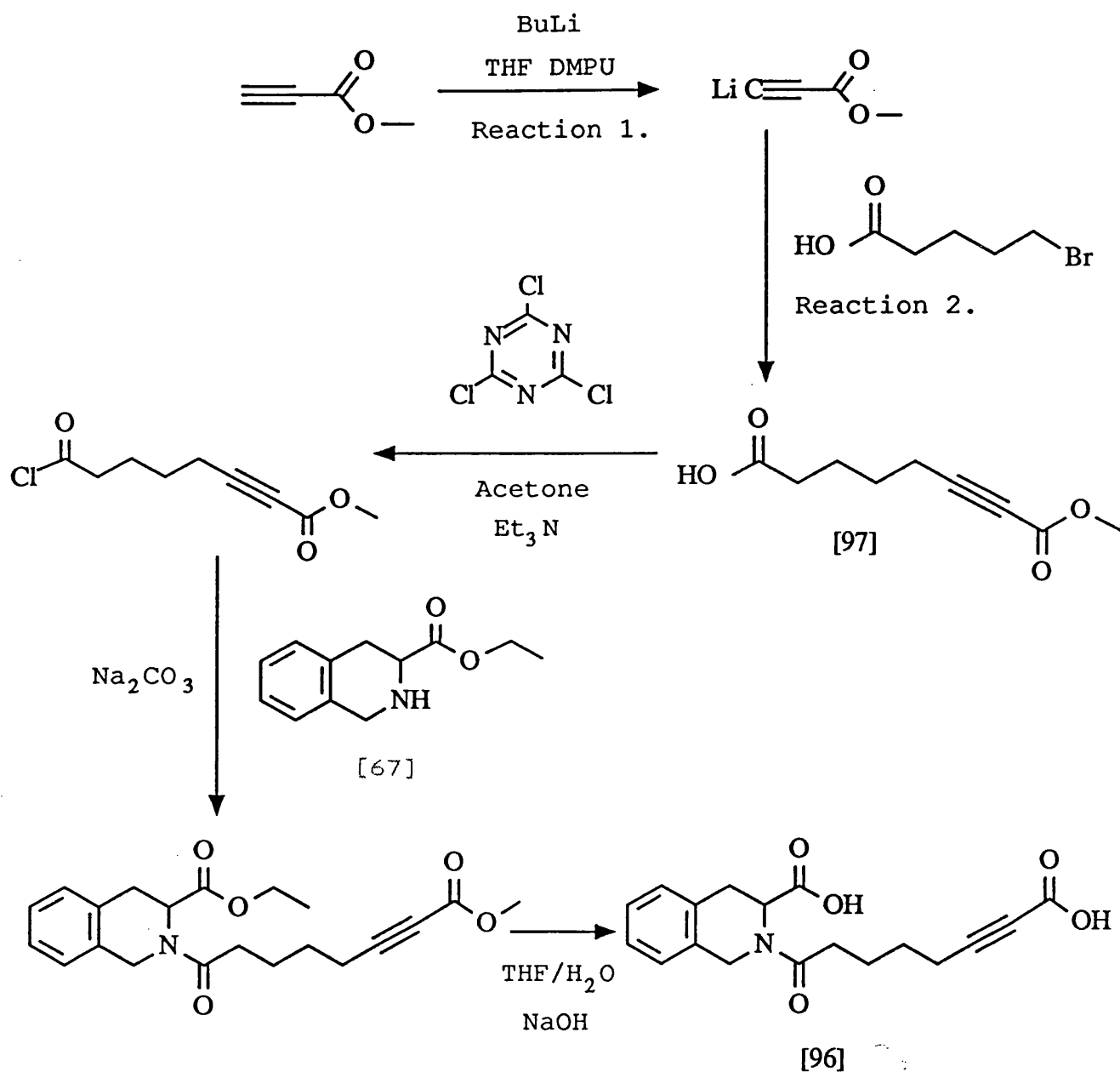
[96]

The initial route selected for the synthesis of [96] was similar to that used in the preparation of [89] and is outlined in figure 40.

Literature precedents^(142,143) exist for the generation of the propiolate anion as in reaction 1. However there was no evidence from the reactions 1 and 2 that the alkynyl acid [97] had been formed. A black oil was isolated from these reactions. This was shown to contain many products by tlc.

A paper reporting that the methyl propiolate anion could only be satisfactorily generated from BuLi at temperatures below -100°C ⁽¹⁴⁴⁾ led us to repeat this reaction at the lower temperature using a THF/ether/pentane (4:1:1) solvent. Again, however a complex mixture of products resulted.

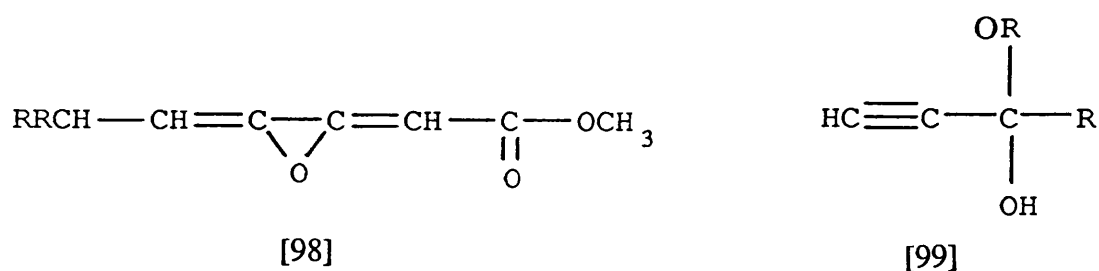
Figure 40.



Results⁽¹⁴⁵⁾ showing that an addition reaction of butyllithium to the carbon-oxygen double bond occurs competitively in the lithium acetylenide forming step caused us to use lithium diisopropylamide instead, as the base in the deprotonation step.

Again the solution turned a dark brown colour. Basic extraction, subsequent reacidification and dichloromethane extraction yielded mostly bromovaleric acid.

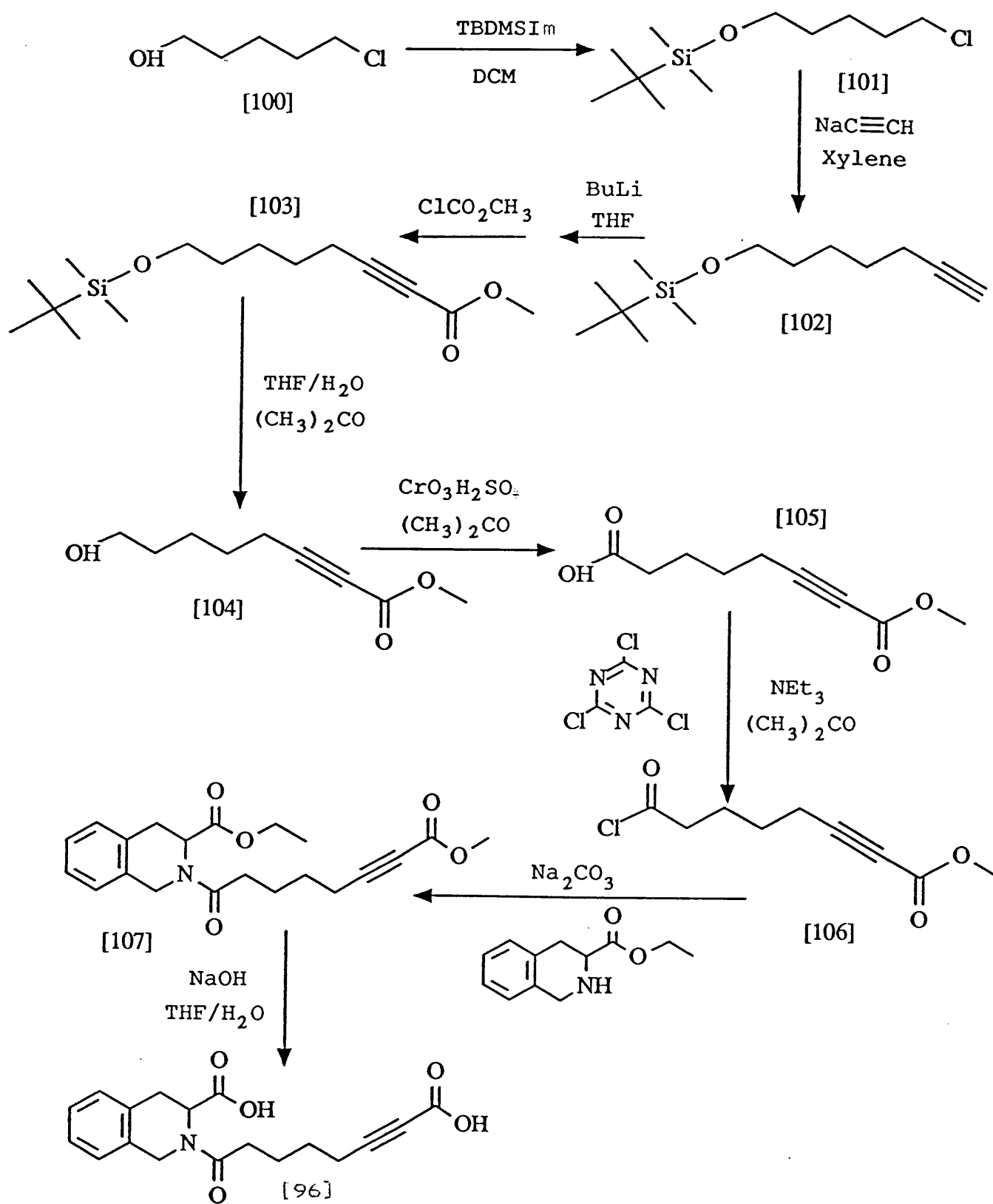
The addition of Grignard reagents to methyl propiolate has been reported to result in Michael-type 1,4-addition reactions and, to a lesser degree, 1,2-addition⁽¹⁴⁶⁾. This results in the formation of compounds of the type [98] and [99] respectively and hence rules out the use of Grignard reagents to deprotonate our substrate.



Another report⁽¹⁴⁷⁾ on the inclination of the alkyl carboxylate and acetylide group of the anion to react with each other prompted a revision of strategy and another route for the generation of [96]. As shown in figure 41.

The first step in the synthesis involves the protection of the hydroxyl group.

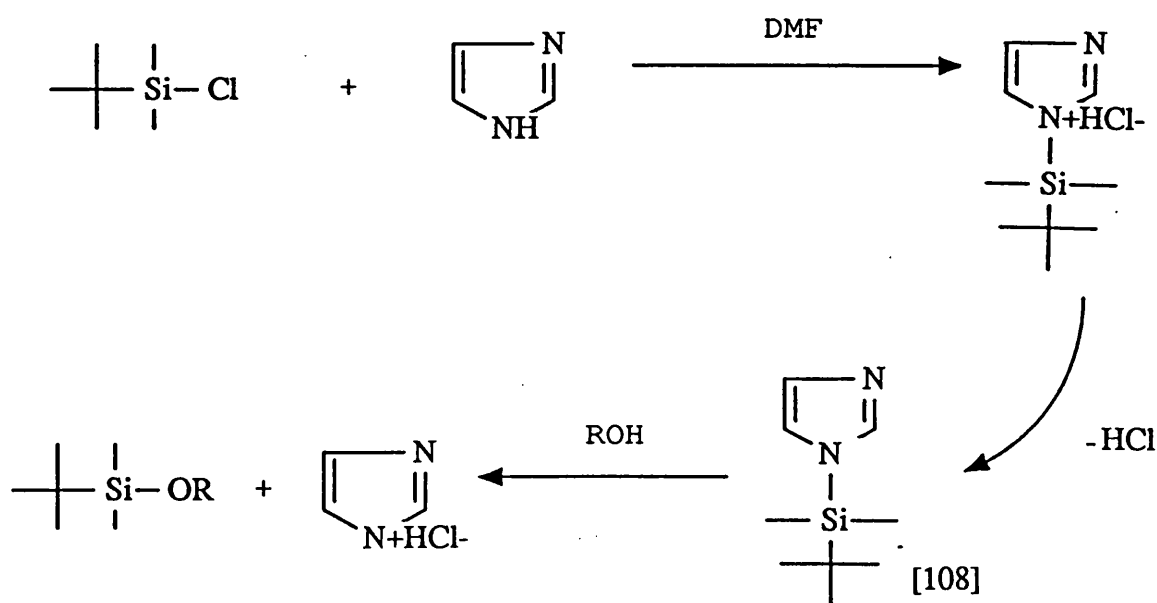
Figure 41.



However trimethylsilyl ethers are rather susceptible to solvolysis in protic media, either in the presence of acid or base. It was therefore decided to use the *t*-butyldimethylsilyl group instead. This more sterically hindered unit often shows greater stability when bonded to an oxygen atom.

The *t*-butyldimethylsilyl group was first introduced by Corey and Venkateswarlu in 1972⁽¹⁴⁸⁾. When *t*-butyldimethylsilyl chloride is used as the silylating agent it is necessary to use imidazole as a catalyst. These reagents react together to form a complex of type [108], shown in figure 42, which is the actual species that reacts with the alcohol⁽¹⁴⁹⁾.

Figure 42.



The high boiling solvent⁽¹⁴⁸⁾ N,N-dimethylformamide (DMF) is necessary for the efficient formation of the complex [108]. However, if N(t-butyldimethylsilyl) imidazole (TBDMSIm) is used as the silylating agent, the much lower boiling and more easily removed solvent dichloromethane can be used.

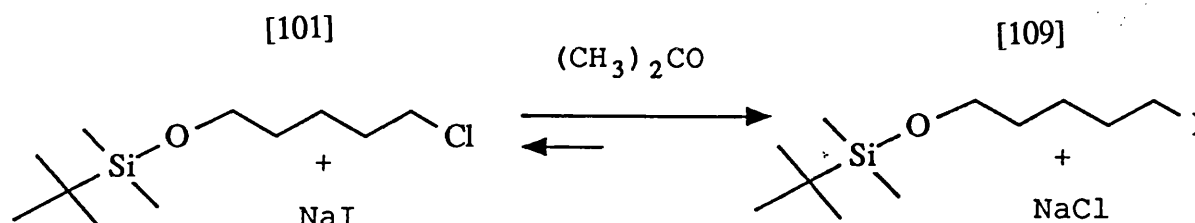
Thus TBDMSIm was added to a solution of 5-chloropentanol in dichloromethane under an atmosphere of nitrogen. After stirring the reaction mixture at room temperature for 18h, the solvent was removed to afford the siloxy chloride [101] in quantitative yield⁽¹⁵⁰⁾.

A solution of [101] under an atmosphere of nitrogen was then added to a stirred suspension of sodium acetylide in xylene at 0°C. The solution was stirred at room temperature for 24h. A mini work up at this stage revealed mostly starting material so the temperature was raised to 30°C for a further 15h. Tlc at this time again showed little conversion to product [102]. The temperature was therefore raised to 80°C for a further 6h. After quenching with ice, the product was isolated in 7% yield.

We attributed the poor productivity of this step to the chloride being an insufficiently good leaving group. It was therefore decided to change it to an iodide by performing a Finkelstein reaction on the siloxy chloride

[101].

Hence, [101], sodium iodide and acetone were heated to reflux for 6h. After work up the siloxy iodide [109] was isolated in 75% yield.



A solution of this iodide was then added to a suspension of sodium acetylide in xylene under an atmosphere of nitrogen. As expected, the iodide proved to be a much more effective leaving group and after stirring at room temperature for 15h the siloxyalkyne [102] was isolated in 63% yield.

Having obtained the alkyne [102] in good yield it was then dissolved in THF, and BuLi was added at -78°C under an atmosphere of nitrogen. After warming to -20°C , to ensure that the anion was formed, and recooling to -78°C , methyl chloroformate was added. Upon work up, the alkynyl ester [103] was obtained in 56% yield⁽¹⁵¹⁾.

The acid labile TBDMS group could be simply removed by treating [103] with a mixture of acetic acid, THF and water (3:1:1) and heating at 85°C for 2.5h. This yielded

the alcohol [104] in 99% yield. The use of tetra-n-butylammonium fluoride to remove the silyl group required three equivalents of this expensive reagent and gave the alcohol [104] in the lower yield of 87%.

The oxidation of the alcohol [104] to the acid [105] was accomplished by adding Jones reagent, a solution of chromic acid and sulphuric acid in water, to a solution of [104] in acetone. This yielded the desired acid in 57% yield.

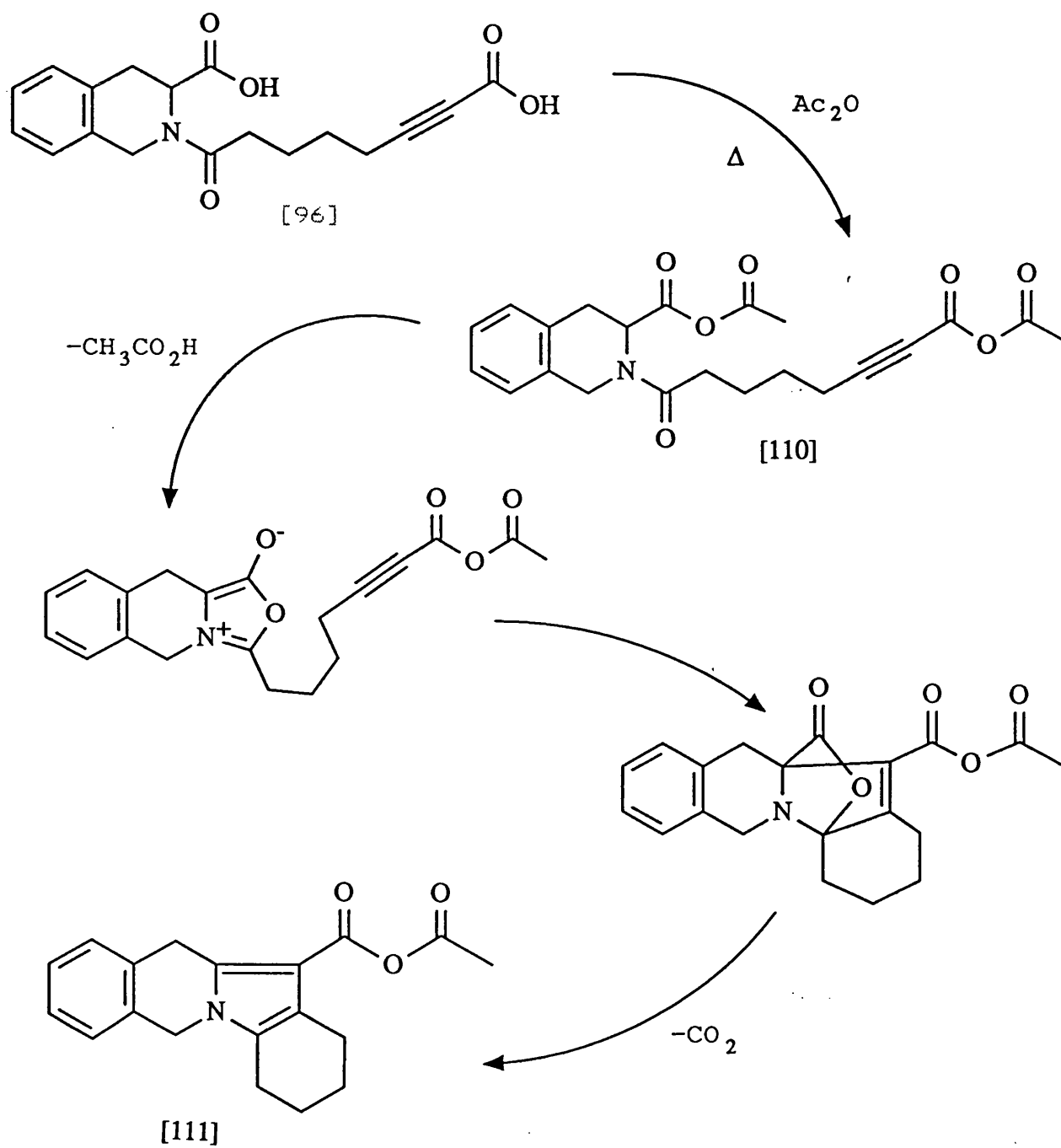
The acid was then dissolved in a solution of cyanuric chloride in acetone and triethylamine and after 1h stirring at room temperature under nitrogen, the isoquinoline ester [67] was added. After a further 14h at room temperature, the racemised isoquinoline amide [107] could be isolated in 58% yield.

The isoquinoline [107] was then dissolved in a solution of THF and water, to which sodium hydroxide was added. The ester groups were saponified and after stirring at room temperature for 1h the isoquinoline acid [96] was isolated in 91% yield.

The intramolecular cyclisation step was next attempted. Hence, the isoquinoline [96] was dissolved in acetic anhydride and heated at 60°C for 2h, during which time the solution became yellow. After the solvent was re

moved, the indenoisoquinoline [111] was isolated in 43% yield. Shown in figure 43.

Figure 43.



The first step in this reaction is the acylation of both the acid groups on the isoquinoline. However, none of the acylated product [110] was isolated, suggesting that once this product was formed, it was very quickly converted to the indenoisoquinoline [111].

The reaction was carried out at high dilution (1 mmol [96]: 50 cm³ solvent) to minimise the chance of intermolecular 1,3-dipolar cycloaddition.

Once success had been achieved in forming a 6-membered and a 5-membered ring through one intramolecular cycloaddition, it was decided to try to form the slightly more strained tetracycle [123], from [121] through this one step reaction. The route to this compound is as outlined in figure 44.

The t-butyldimethylsilyl group was again used to protect the hydroxyl group. Hence, TBDMSIm was added to a solution of 4-chloro-1-butanol in dichloromethane under an atmosphere of nitrogen. After stirring at room temperature for 18h the siloxy chlorobutane [113] was isolated in 98% yield.

The poorer chloride leaving group was exchanged for an iodide using the Finkelstein reaction. Sodium iodide was added to a solution of the chlorobutane [113] in acetone. After heating at reflux for 16h, the iodobutane

[114] was isolated in 77% yield.

Figure 44.

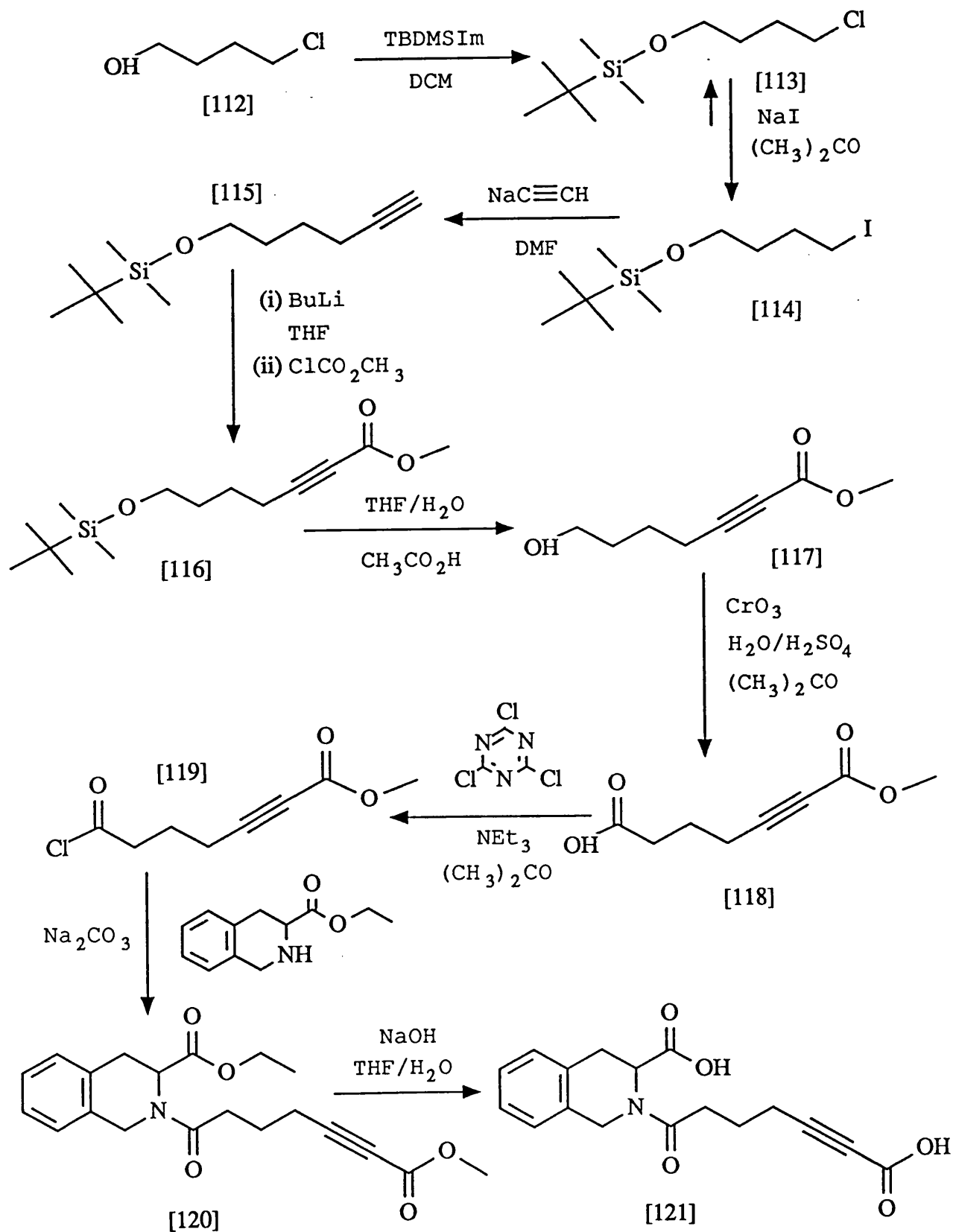
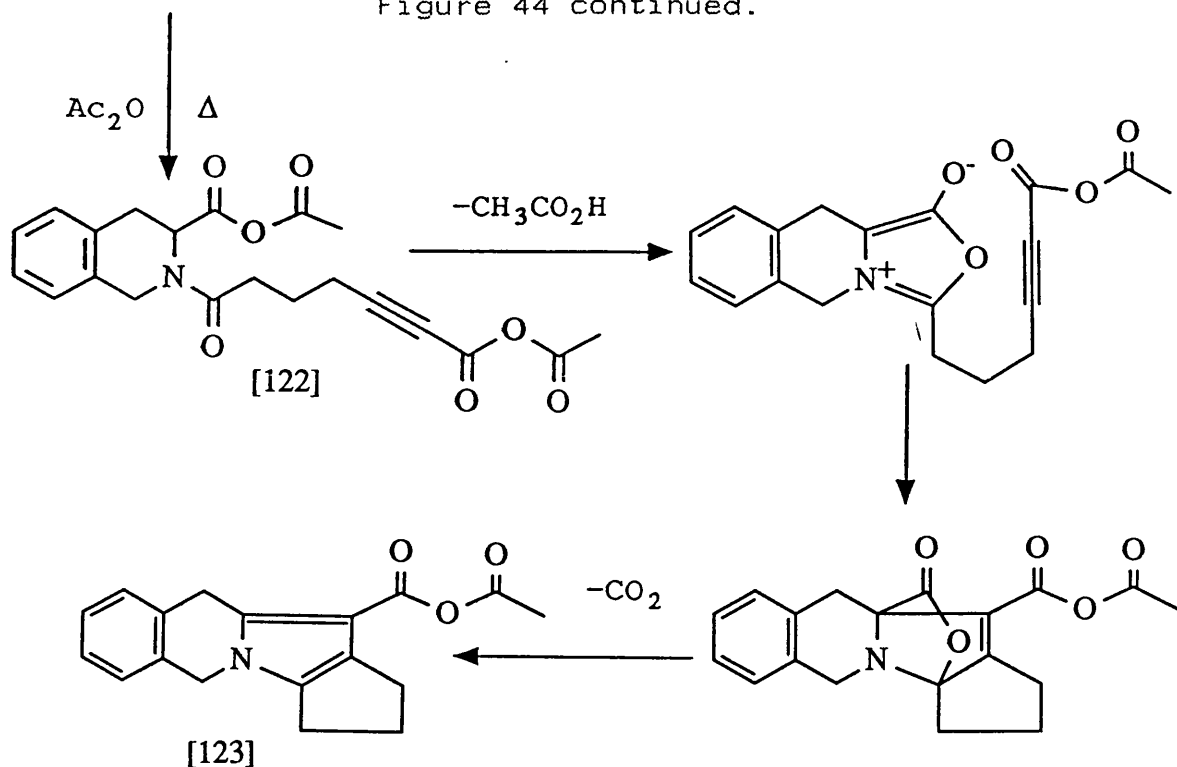
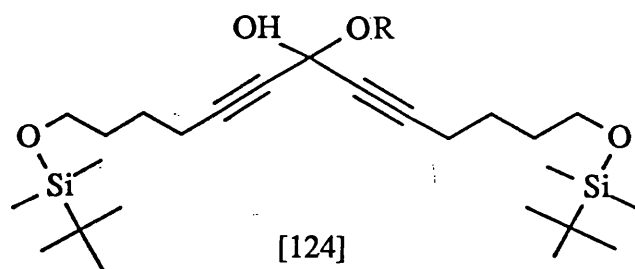


Figure 44 continued.



The iodide ion was then displaced by treatment of a solution of [114] in DMF with 18% sodium acetylide solution in xylene at room temperature for 16h. Upon work up, the alkyne [115] was obtained in 60% yield.

The anion of this alkyne was obtained by treating a solution of [115] in THF at -78°C with BuLi. Methyl chloroformate was then added and the chloride ion displaced by reaction with the acetylide anion. This yielded the alkynyl ester [116] in the rather disappointing yield of 45%. In retrospect it might have been better to have performed an inverse addition of the acetylide anion to an excess of the methyl chloroformate, to lessen the chance of the acetylide anion reacting with the product [116] to form the alcohol [124].



The t-butyldimethylsilyl group was effectively removed by treating a solution of the silyl ether [116] in THF and water with acetic acid at 80°C for 1.5h. This liberated the alcohol [117] in almost quantitative yield.

The alcohol was converted into the acid by treatment with Jones reagent for 1h at room temperature. The acid [118] was obtained in 54% yield.

The acid [118] was then converted to the acid chloride by adding it to a solution of cyanuric chloride in acetone and triethylamine and stirring at room temperature for 1.5h. The isoquinoline [67] was then added and after a further 15h at room temperature, the triazine derivative was filtered off and the isoquinoline amide [120] isolated in 63% yield.

To enable the better leaving group, the anhydride, to be formed at position C-3, the ester group was saponified by treating a solution of the isoquinoline [120] in THF with a solution of sodium hydroxide in water. After stirring at room temperature for 2h the isoquinoline acid [121] was isolated in 82% yield.

The cyclisation step was next attempted. The isoquinoline acid was dissolved in acetic anhydride and after 3hrs at 70°C the solvent was removed to leave the cyclised product [123] in 37% yield.

The slightly higher temperature and longer reaction time necessary to effect a reasonable yield of cyclised product on this occasion is probably a reflection of the increased difficulty in forming two five membered rings rather than the five and six membered rings in product [111]. Although forming the transition state on the route to compound [111] requires a greater loss of entropy than does the corresponding transition state for compound [123], the five membered ring has a restricted conformation and more ring strain than the six membered ring. This is reflected in the lower free energy of formation of cyclohexane over that of cyclopentane.

In subsequent scale up of the reactions leading to compounds [111] and [123], a short cut to forming the *t*-butyldimethylsiloxy iodides was employed. The first two steps, namely the conversion of the chloroalcohol to the *t*-butyldimethylsilylchloride and the subsequent substitution to form the iodide, can be replaced by a one step reaction.

For this step the more expensive chloroalcohols can be replaced by the cheaper cyclic ethers tetrahydropyran

and tetrahydrofuran. To form 1-(t-butyldimethylsilyl)-5-iodopentane [109], t-butyldimethylsilylchloride, and sodium iodide, in acetonitrile are reacted together to form t-butyldimethylsilyliodide¹⁵². This in situ formation of the silicon-iodide bond circumvents the problems associated with its hydrolytic susceptibility which is a deterrent to its prolonged storage.

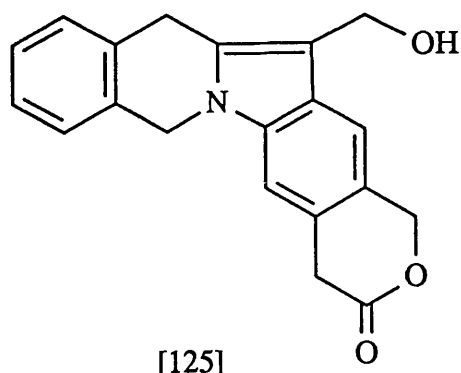
Such a reaction was first reported by Olah¹⁵³ when trimethylsilyl iodide was used to cleave a variety of esters, lactones, carbamates and ethers. It was found that cleavage of esters and lactones occurred more slowly with this reagent than with preprepared reagent. This was postulated to be due to the presence of hydroiodic acid as an impurity in preprepared reagent.

Having formed the silyl iodide, tetrahydropyran was added along with imidazole, to keep conditions basic, and the solution was stirred for 18h at 50°C. This gave the product [109] in 80% yield.

To form 1-(t-butyldimethylsilyl)-4-iodobutane¹⁵⁴, the same reagents were used, substituting tetrahydrofuran for tetrahydropyran. For optimum yield the reaction was heated at 55°C for 10h, after which time the product [114] was isolated in 83% yield.

After the success achieved in forming the cyclised

products [111] and [123], it was decided to form the more complicated pentacycle [125].



This pentacycle has a structure which is similar to both camptothecin and mitoguadone, and as such could, we thought, perhaps possess some kind of anti-neoplastic properties.

The theoretical route to this compound posed some interesting synthetic challenges and is outlined in figure 45.

The route to this target starts with 2,2,6-trimethyl-1,3-dioxenone [126]. This compound was first isolated in 1953¹⁵⁵ from the reaction of diketene with acetone when heated with a catalytic amount of *p*-toluenesulphonic acid.

It functions as an acetoacetylating agent¹⁵⁶ when reacted with alcohols and this acts as a β -keto ester synthon¹⁵⁷. Although it is much more reactive than acetoacetate esters, it is much less reactive than diketene

Figure 45.

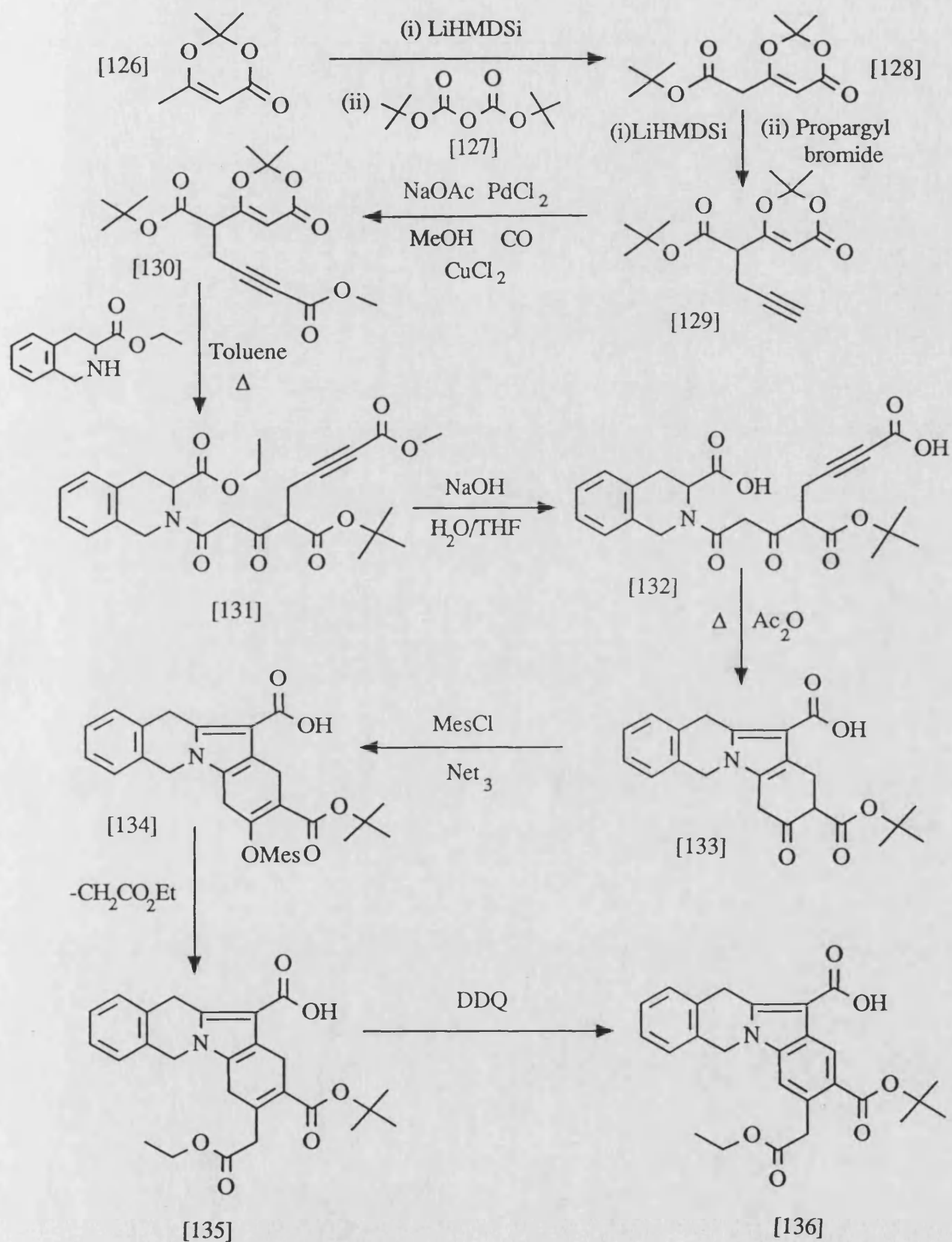
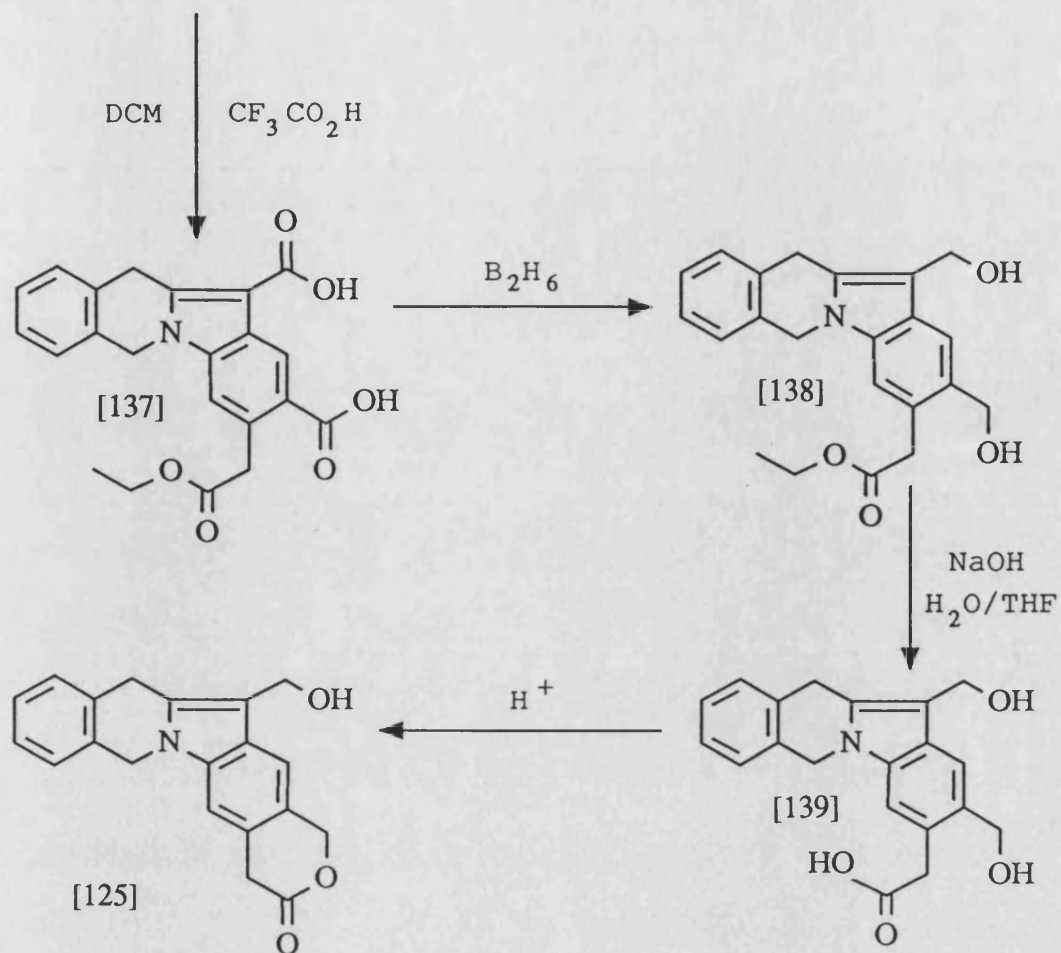


Figure 45 continued.



itself. Its advantage over diketene lies in its easy handling and storage. It also lacks the toxicity associated with diketene.

The first step was to form the lithium dienolate and acylate this at the gamma position to form the t-butyl ester [128]. As shown in figure 45.

Much has been written on the propensity of lithium dienolates of alpha, beta-unsaturated carbonyl compounds to alkylate predominantly at the alpha position.^{158,159,160} The use of copper(I) as the counter ion results in a preference for gamma-alkylation over alpha-alkylation, although this trend is more noticeable in alpha,beta-unsaturated acids than in the corresponding esters.^{161,162,163}

Some interesting work by A.B.Smith^{164,165} however, showed that in certain cases β -alkoxy-alpha,beta-unsaturated carbonyl compounds could be made to undergo exclusive alkylation at the gamma-position.

In their work they investigated the alkylation of lithium dienolates derived from substituted 3(2H)-furanones and found that exclusively gamma-alkylation occurred if the furanone was fully substituted at the alpha' position. A series of related compounds were then investigated and the general rule that emerged was that gamma alkylation occurred every time the corresponding lithium dienolate possessed a double bond which was exocyclic to a ring. As shown by the examples in figure 46.

In a trial reaction butyllithium was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane in THF. 2,2,6-Trimethyl-1,3-dioxen-4-one was added to this

at -78°C and after 2h the solution was quenched with D_2O . This did indeed yield the gamma substituted product [140], shown in figure 47, in 64% yield.

Figure 46.

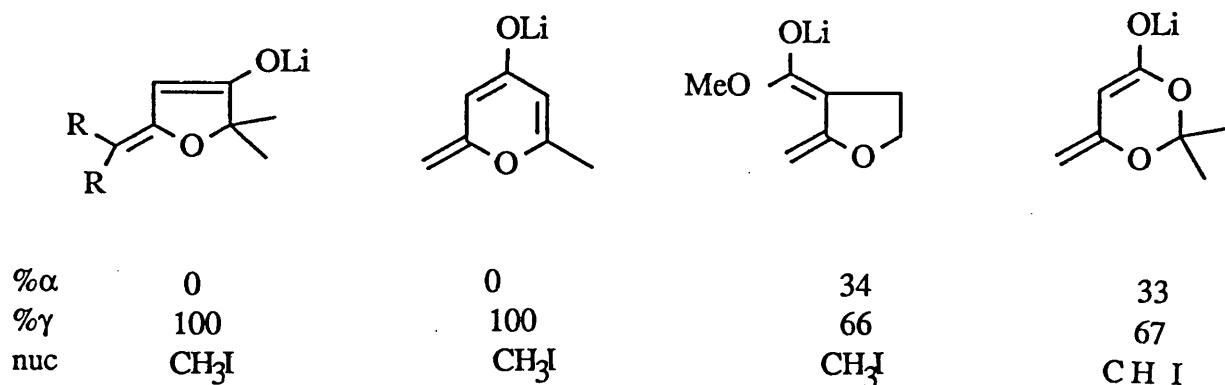
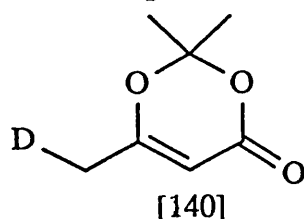


Figure 47.



Since no literature precedent existed for the acylation of the dioxenone [126], the method employed by A.B.Smith⁽¹⁶⁵⁾ for the alkylation was used, with lithium diisopropylamide as the deprotonation agent.

In subsequent reactions it was found that the use of lithium hexamethyldisilazide (LHMDS) as the deprotonation agent resulted in a higher yield of product.

Hence butyllithium was added to a stirred solution of hexamethyldisilazane in THF under nitrogen at 0°C . After 30 minutes, the temperature was reduced to -78°C and the dioxenone [126] was added. The solution was warmed to 0°C

for 30 minutes then cooled to -78°C and di *t*-butyldicarbonate [127] was added. After 1h, the solution was warmed to room temperature. This resulted in the gamma acylated product [128] being produced in 76% yield.

The next step was to alkylate this product, again at the gamma position. LHMDs was formed as before. The acylated product [128] was then added and the solution warmed to 0°C then cooled to -78°C and propargyl bromide added. After 1h the solution was warmed to room temperature and quenched with saturated ammonium chloride solution. This resulted in the formation of a complex mixture of products.

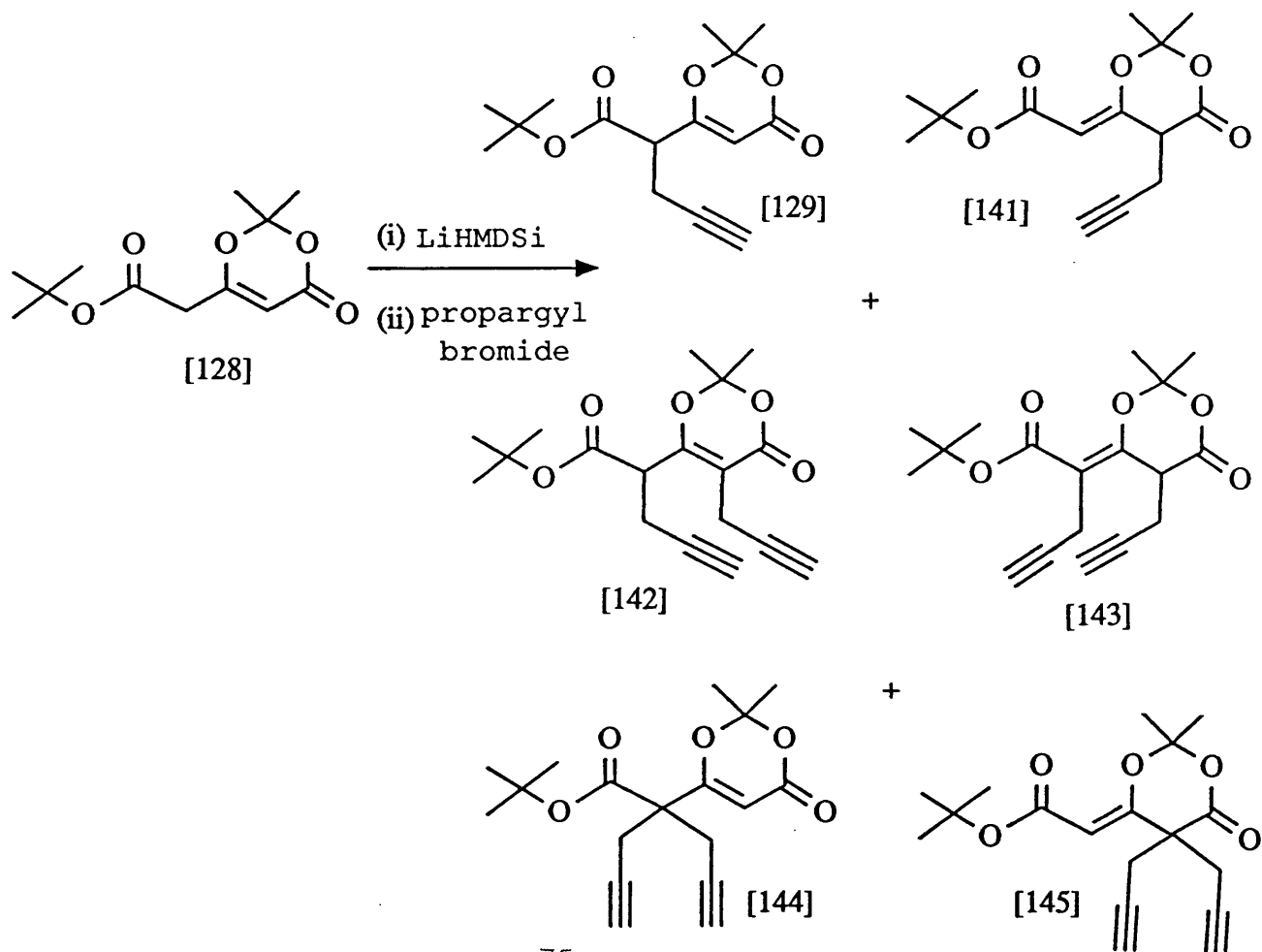
The reaction was repeated, this time keeping the temperature at -78°C throughout and quenching at this temperature as well. Again a mixture of products was produced.

We had hoped for selectivity in this reaction but mass spectrometric evidence showed that both mono and dialkylated material were present. Much work was undertaken to try and isolate these materials in the pure state and to identify them. However the effort was to no avail, since although relatively pure samples of mono alkylated compounds and dialkylated compounds were obtained each consisted of isomeric mixtures.

In retrospect, the formation of isomeric alkylated products seems assured, since by acylating the dioxenone to give the starting material for our experiment we might have expected the activities of the endo and exo sites to be similar. Both are now adjacent to a carbonyl group so that the mesomeric anion generated by treating the acylated dioxenone with base has the potential to alkylate in two directions to give two different monoalkylated products [129] and [141], as shown in figure 48.

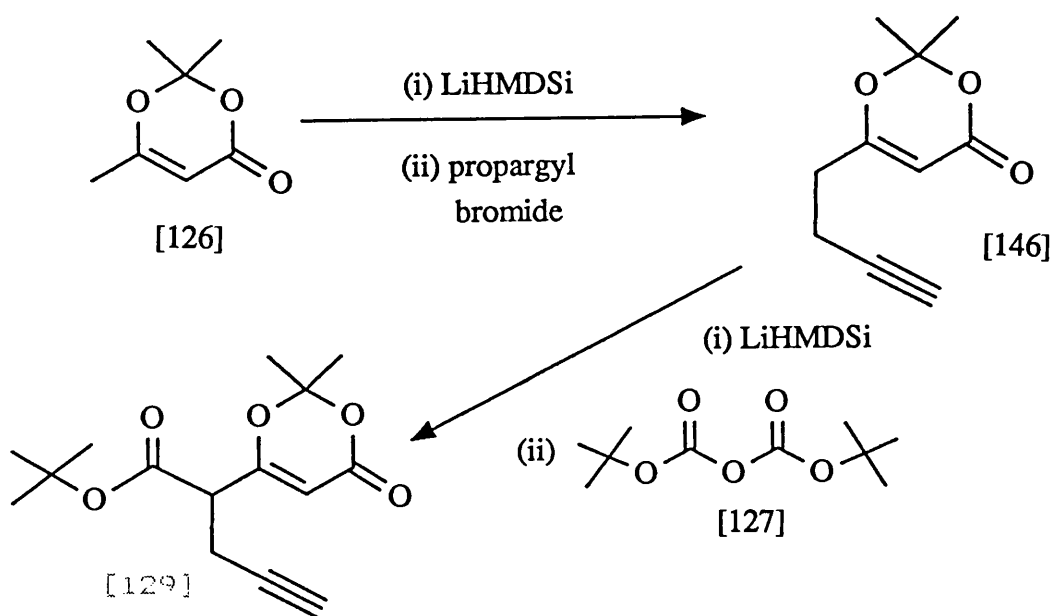
A second deprotonation may now generate a second mesomeric anion which, again, may alkylate at two sites, producing a total of four different dialkylated products, [142]-[145].

Figure 48.



Since so many problems were encountered with this sequence of reactions it was decided to try a different route to [129], this time alkylating first and then acylating the product, as shown in figure 49. This method would remove the problems of equivalence of the positions alpha and gamma to the carbonyl group in the dioxenone and hopefully prevent dialkylation.

Figure 49.



LiHMDS was prepared as before, and the temperature of the reagent mixture was reduced to -78°C . The dioxenone was then added and, after warming to 0°C and recooling to -78°C , HMPA and propargyl bromide were added. This gave product [146] but the yield was very poor, only 17%.

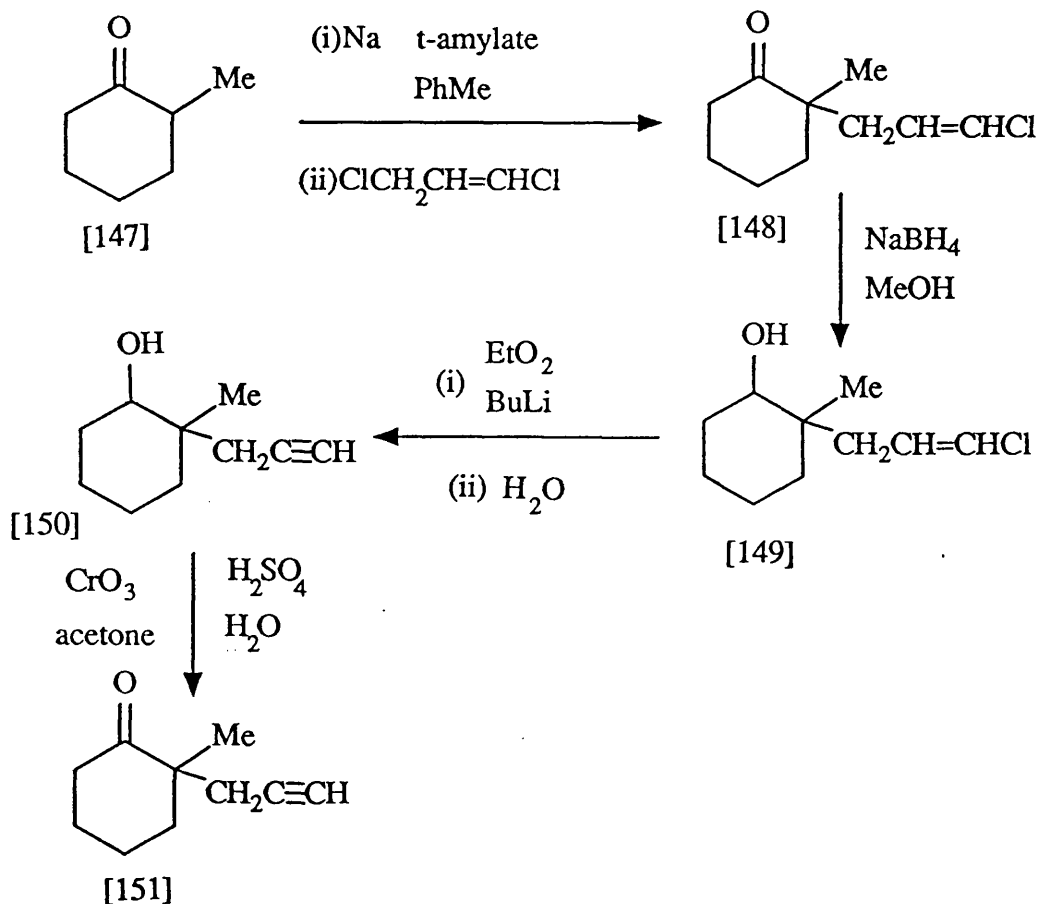
The reaction was repeated keeping the temperature at -78°C throughout but the yield in this case was worse at

under 10%. These low yields are probably attributable to the instability of propargyl bromide in a strongly basic medium.¹⁶⁶

A couple of methods of circumventing this problem were illustrated by R.B.Millar.¹⁶⁷ In the course of his work on the synthesis of the gibberellic acid skeleton it was necessary to attach a propargyl group to a substituted cyclohexanone. It was found that direct alkylation with propargyl bromide gave poor yields, so two other methods were employed.

The first of these is as outlined below in figure 50.

Figure 50.



The cyclohexanone [147] was initially alkylated with 1,3-dichloropropene. The carbonyl group was then reduced to the alcohol [149] and then the vinyl chloride was converted to the acetylene [150] by dehydrochlorination with butyllithium. Finally the alcohol was oxidised back to the carbonyl group. This gave product [151] in 26% overall yield.

The second method used 3-bromo-1-trimethylsilyl-1-propyne as the propargylating agent and this, followed by desilylation gave the product [151] in 50% overall yield.

The method used for making the 3-bromo-1-trimethylsilyl-1-propyne started with propargyl alcohol. The hydroxyl group of this was protected as a tetrahydropyranyl ether. This protected material was deprotonated with methyllithium and then silylated with trimethylsilylchloride. The tetrahydropyranyl group was then removed in refluxing methanol with *p*-toluenesulfonic acid and the product was then brominated with phosphorus tribromide.

Due to the known high acid sensitivity of the trimethylsilyl group it seems likely that during the removal of the tetrahydropyranyl group some desilylation would occur. For this reason it was decided to use a *t*-butyldiphenylsilyl¹⁶⁸ (TBDPS) group as protection for the alkynyl position.

Figure 51.

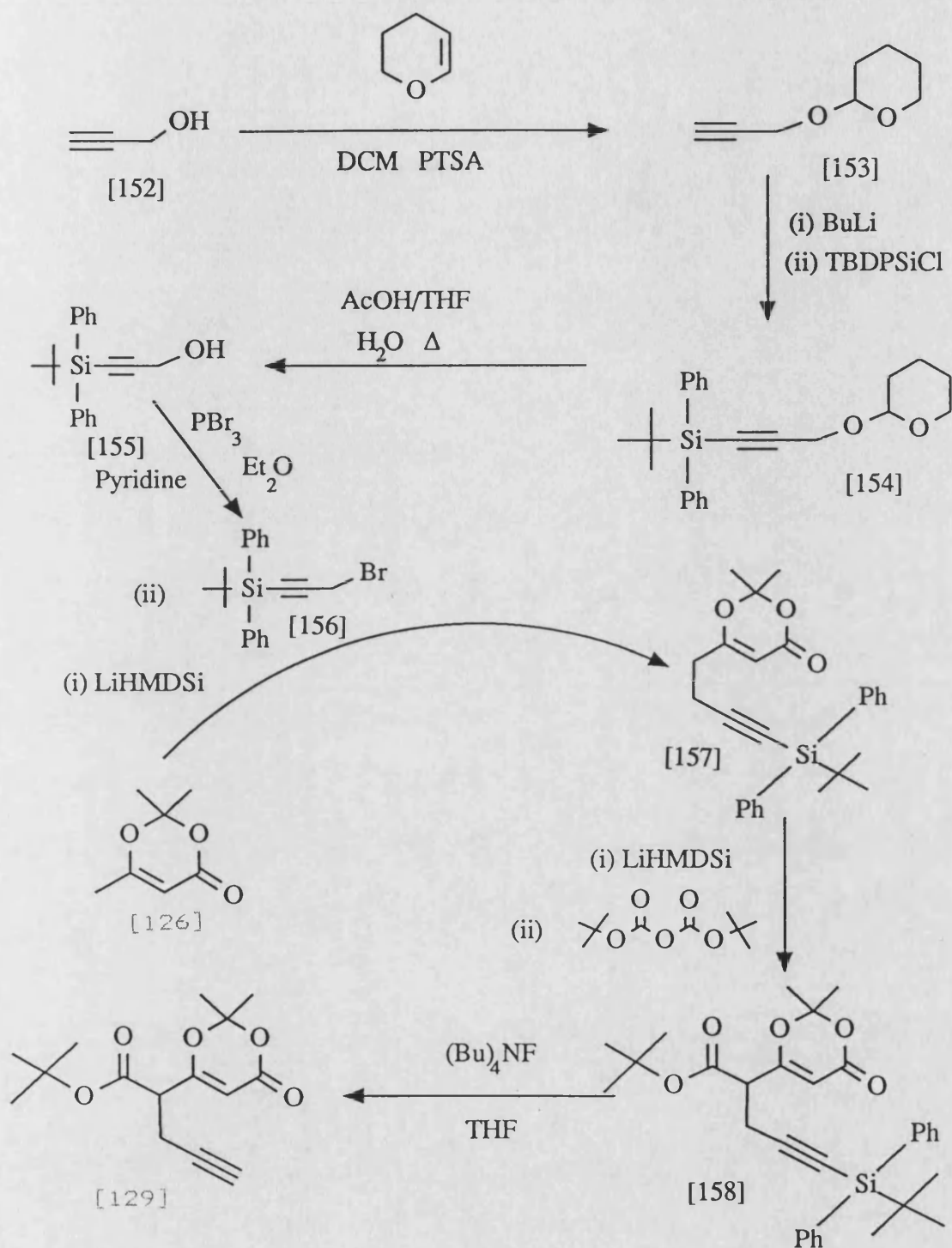


Figure 51 outlines our new route to product [129].

Hence, to a solution of propargyl alcohol [152] and 3,4-dihydro-2H-pyran¹⁶⁹ in dichloromethane at 0°C was added a catalytic amount of *p*-toluenesulfonic acid. Upon work up the product [153] was produced in almost quantitative yield.

This product was then stirred with a solution of butyllithium in THF at -78°C for 30 minutes. TBDPS chloride was added and after 2h the solution was warmed to room temperature and quenched with ammonium chloride solution. The silylated product [154] was isolated in 95% yield.

The tetrahydropyranyl group was next removed by stirring the product in a solution of acetic acid, THF and water for 4h. After work up this yielded the alcohol [155] in 89% yield.

The alcohol group was then substituted with a bromine atom by adding phosphorus tribromide to a solution of [155] in ether, containing a catalytic amount of pyridine.¹⁷⁰ After stirring for 2h at room temperature and work up, the brominated product [156] was isolated in 90% yield.

This was then attached to the dioxenone [126]. The dioxenone was first added to a solution of LHMDs at -78°C and after warming to 0°C and recooling to -78°C, the

bromide [156] was added. After 2h the solution was quenched and the product [157] was produced in 81% yield.

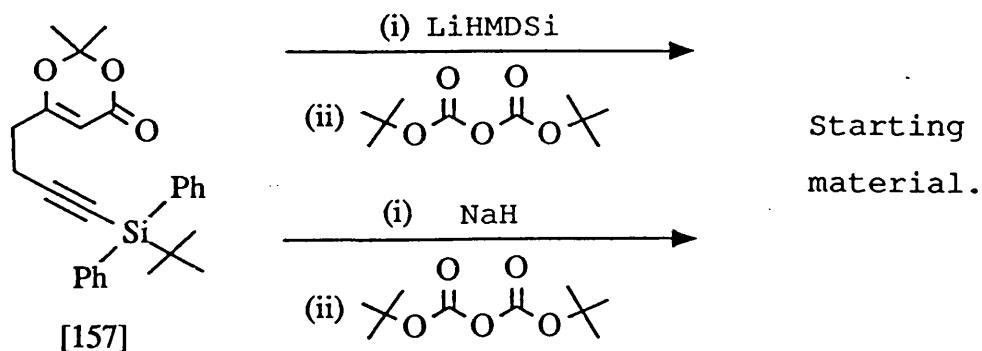
The next step was to acylate this product at the gamma position. Since the acylation of the dioxenone [126] occurred in good yield, the same method was employed for the acylation of the substituted dioxenone [157].

Hence [157] was added to a solution of LHMDS in THF at -78°C . The solution became a dark red colour and after 30 minutes di-*t*-butyldicarbonate was added. Upon work up however, only starting material was present.

The reaction was repeated, this time raising the temperature to 0°C for 30 minutes once the dioxenone [157] had been added and then lowering it to -78°C before the addition of the di-*t*-butyldicarbonate. Again only starting material was present after work up.

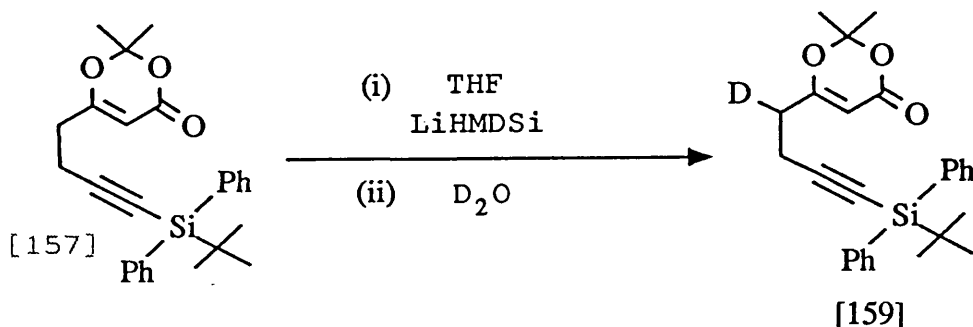
To check if steric hindrance was the reason why the reaction failed with lithium hexamethyldisilazide, the experiment was repeated, as shown in figure 52, this time using sodium hydride as the deprotonating agent. This also proved unsuccessful.

Figure 52.



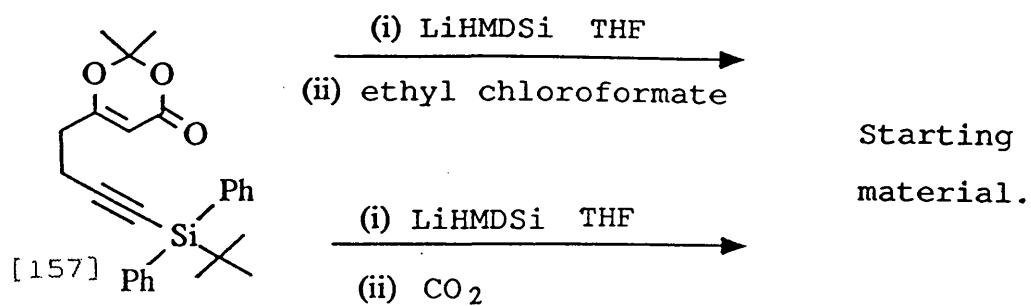
The reaction was repeated with lithium hexamethyldisilazide as the base but this time quenching with deuterium oxide. Upon work up the desired gamma deuterated product [159] was isolated, thus proving that the anion was indeed being formed with this base.

Figure 53.



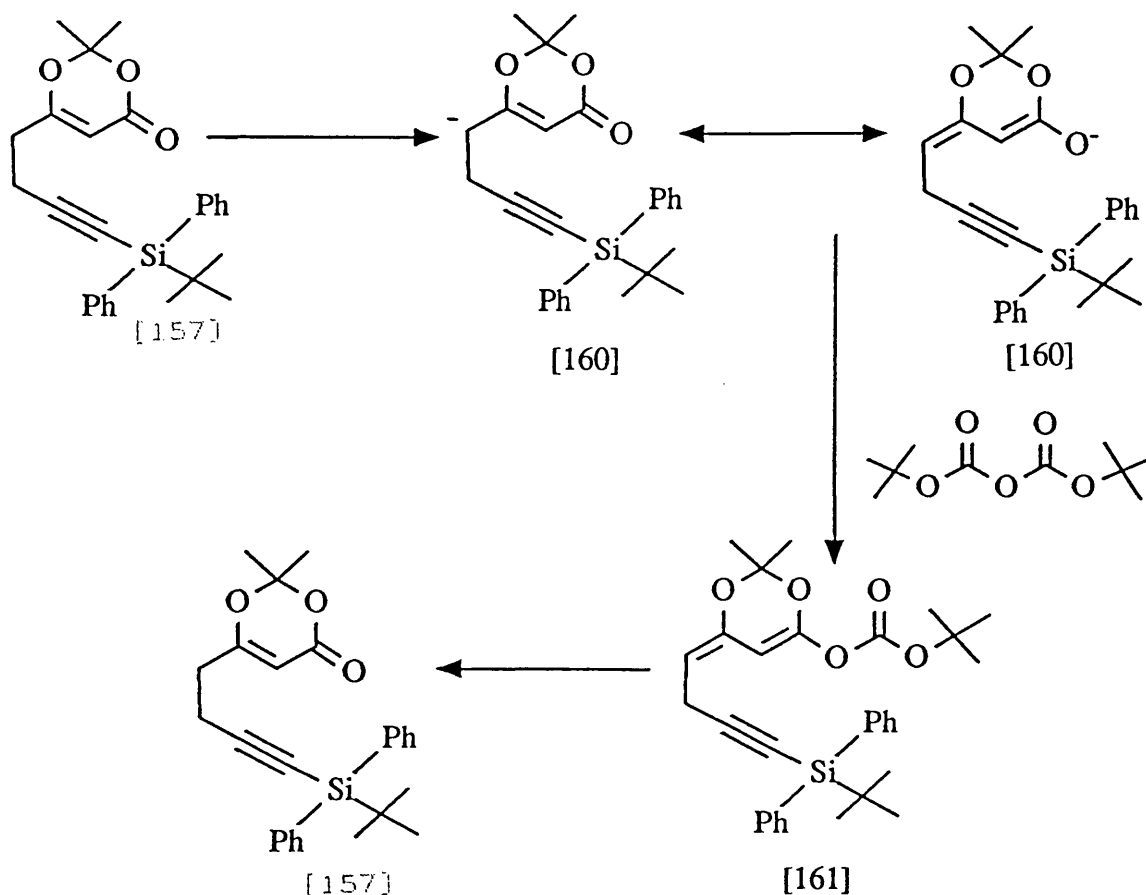
To check whether the dioxenone was not acylated with the di-*t*-butyldicarbonate due to the steric hindrance of this reagent, the reaction was repeated using ethyl chloroformate as the acylating agent. Again only starting material was obtained upon work up, and the same result was obtained using solid carbon dioxide as the acylating agent.

Figure 54.



It seems likely that what is taking place in these reactions is that rather than carbon acylation, oxygen acylation is occurring to form the enol ester [161], and upon work up this is hydrolysed and the original diox- none is regenerated, as shown in figure 55.

Figure 55.

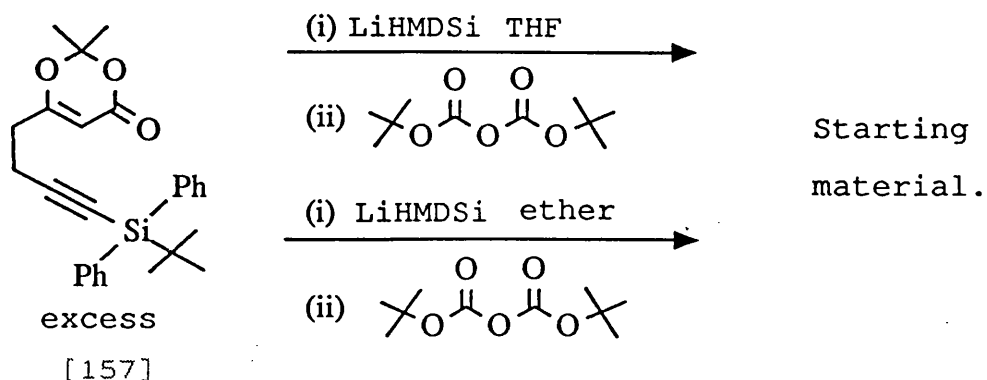


The solvent, tetrahydrofuran, being polar and aprotic, will not greatly solvate either the oxygen or the carbon of the ambident anion [160], which will tend to encourage attack by the more electronegative oxygen.

The lithium cation, however, being small and with no unshared pairs of electrons in its valence shell, is a hard acid, and as such would be expected to be bound quite tightly to the oxygen atom of the ambident dioxenone anion, hence encouraging attack of the di-*t*-butyldicarbonate at the less hindered carbon atom. The fact that the reaction with the dioxenone [126] acylated in good yield at the carbon atom under the same conditions, also makes it strange that carbon acylation does not occur with the substituted dioxenone [157].

In an attempt to increase the proportion of carbon over oxygen acylation, a three fold excess of the dienolate anion [160] was used, with the hope that once the oxygen acylated product had been formed, carbon acylation would then have the chance to occur to form [158]. Again though, only starting material was present upon work up.

Figure 56.



To circumvent this problem it was decided to perform the acylation at a later stage, once the dioxenone had been attached to the isbquinoline [67]. It also seemed logical to perform the acylation of the alkynyl position at the same time, hence reducing the number of reaction steps by one.

The modified route to this product [165], which is slightly different to [132] in that the alkynyl position will now be protected with a *t*-butoxycarbonyl group rather than an ethoxycarbonyl group, is shown in figure 57.

Figure 57.

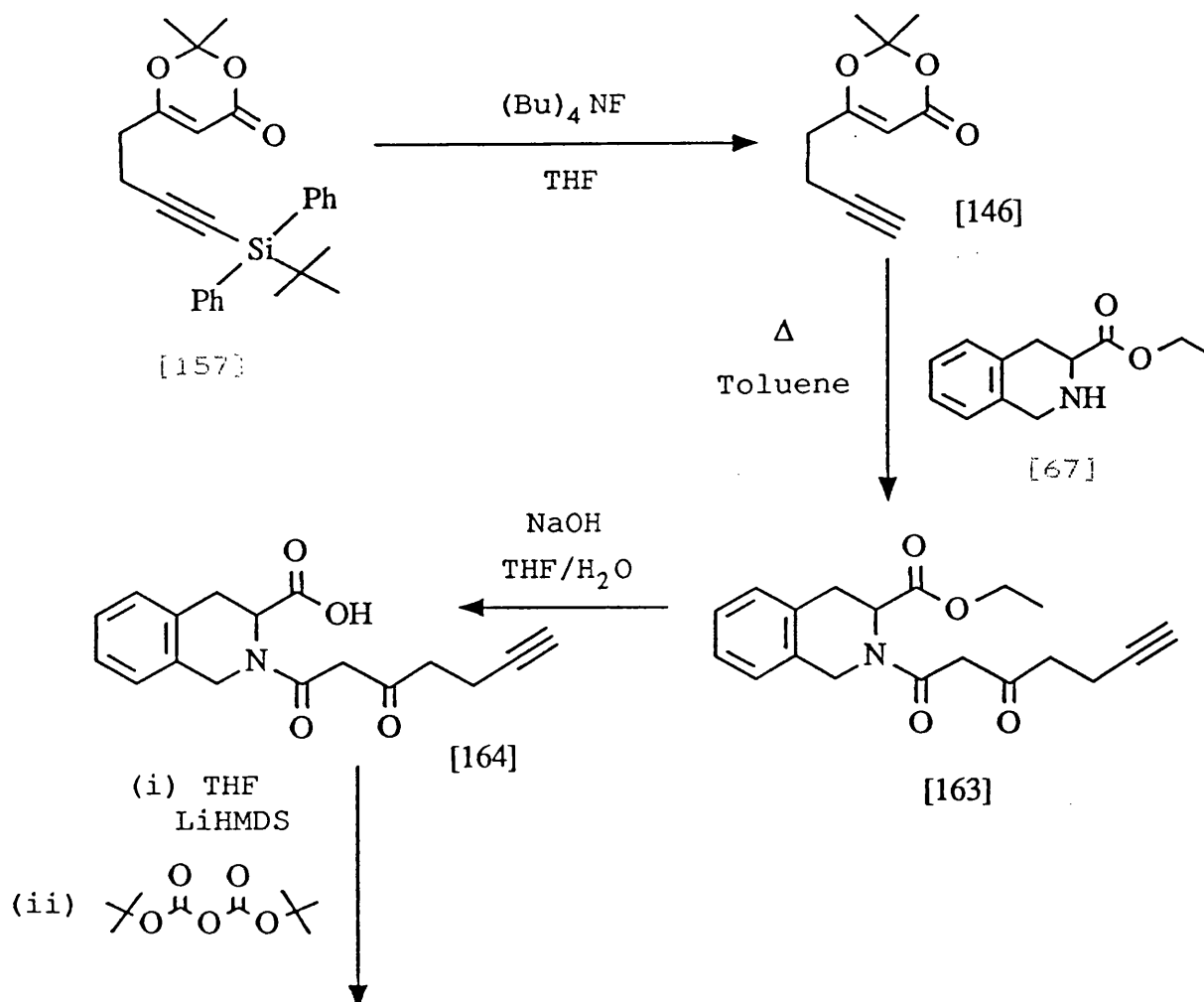
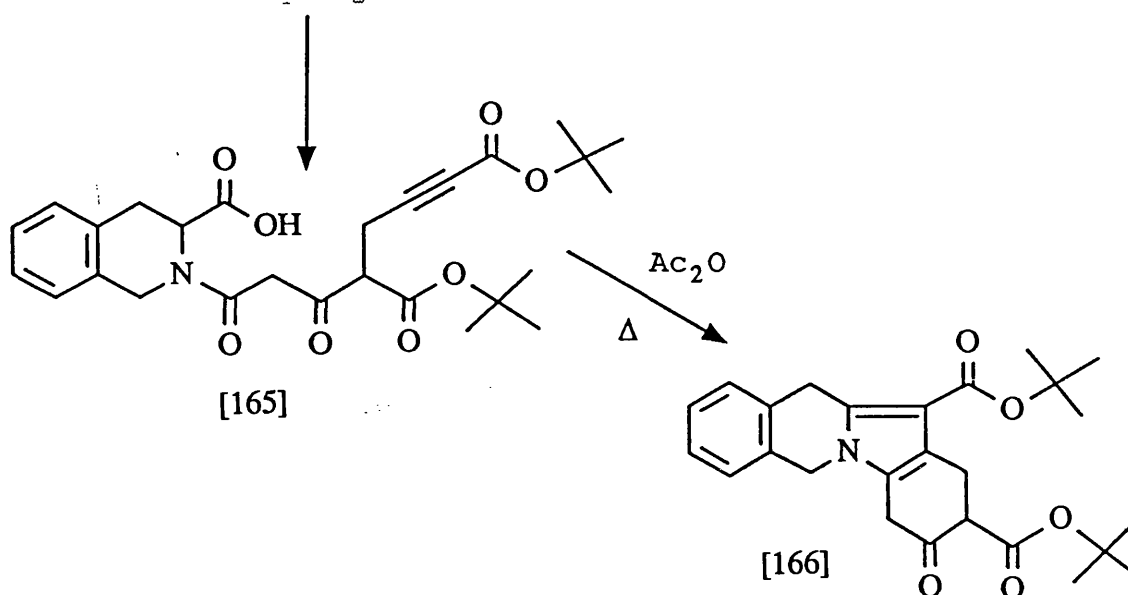


Figure 57 continued.

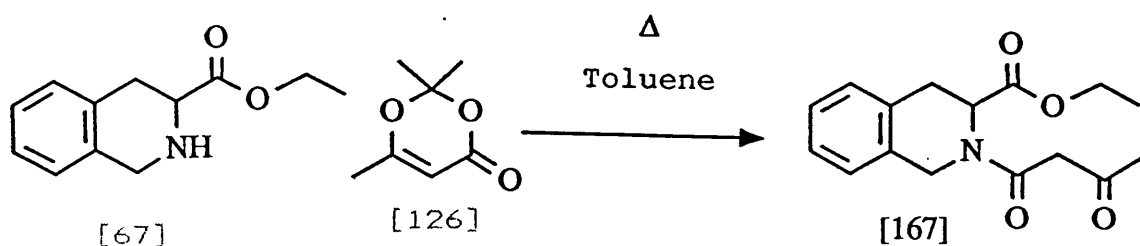


The slightly increased bulkiness of the alkynyl protecting group would not be expected to hinder the cyclisation step however, since the reaction works perfectly well between the isoquinoline [67] and the bulkier 1,3-dipolarophile, benzyldiene malononitrile.

The silyl protecting group on [157] was next removed¹⁶⁸. The compound was added to a solution of tetrabutylammonium fluoride in tetrahydrofuran. After stirring at room temperature for 3 hours and subsequent work up, the product [146] was isolated in 66% yield.

The next step was the addition of this compound to the isoquinoline [67]. A trial reaction was first performed using the unsubstituted dioxenone [126] and the isoquinoline [67] as shown in figure 58.

Figure 58.



The method used was the same as that used by Boeckman and Perni¹⁷¹ in the course of their work to form acyltetramic acids. The isoquinoline ester and an equimolar amount of the dioxenone were heated at reflux in a solution of toluene for 5 hours. This yielded the acylated product [167] in 62% yield. This yield was markedly lower than the best yield that the above authors reported in their paper for the acetylation of rather more complicated secondary amines than isoquinoline.

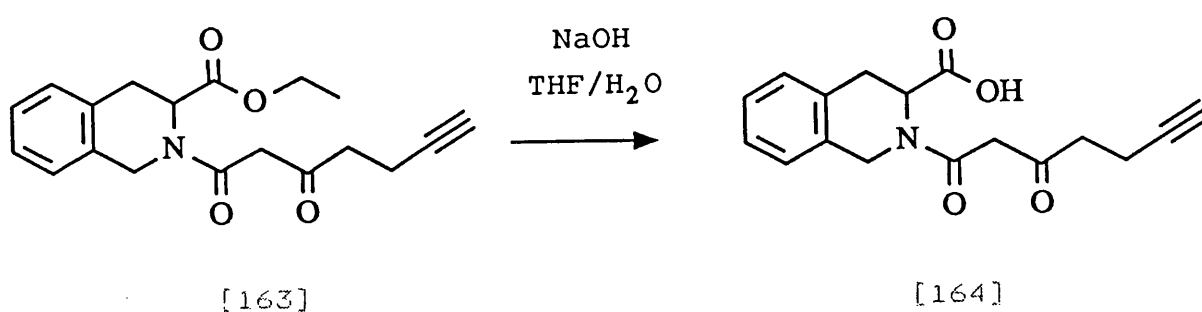
Another paper by Boeckman¹⁷², again concerning the acetylation of secondary amines, reported that this procedure occurred in good yield if xylene was used instead of toluene as the reaction medium.

When the isoquinoline [67] and dioxenone [126] were heated in a solution of xylene at reflux for 1 hour, the acylation occurred to give product [167] in a much enhanced 83% yield.

Hence, a solution of the dioxenone [146] and the isoquinoline [67] in xylene was heated for 3 hours at

reflux, during which time the solution became brown. After work up the acylated product [163] was isolated in 63% yield.

The next step was to hydrolyse the ester grouping to an acid. This was accomplished by the addition of sodium hydroxide to a solution of the isoquinoline [163] in tetrahydrofuran and water. After 1.5h at room temperature the isoquinoline acid [164] was obtained in very good yield.



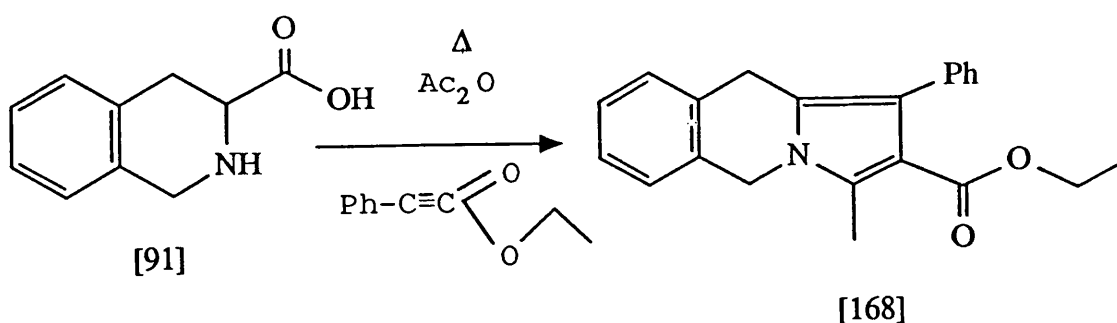
Unfortunately, due to time limitations, this was as far as work progressed on this line of research.

While this work was in progress, further reactions were performed to investigate the performance of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid in 1,3-dipolar cycloaddition reactions. Hence, phenylacetylene was added to a solution of the isoquinoline [91] in acetic anhydride. Upon heating, the solution became black and t.l.c. showed the presence of many close running spots.

The use of propargyl bromide as the dipolarophile in a similar reaction produced the same result, even though work by Huisgen⁽¹²⁰⁾ has shown that dipolarophiles possessing electron withdrawing groups are more reactive and usually lead to isolable products.

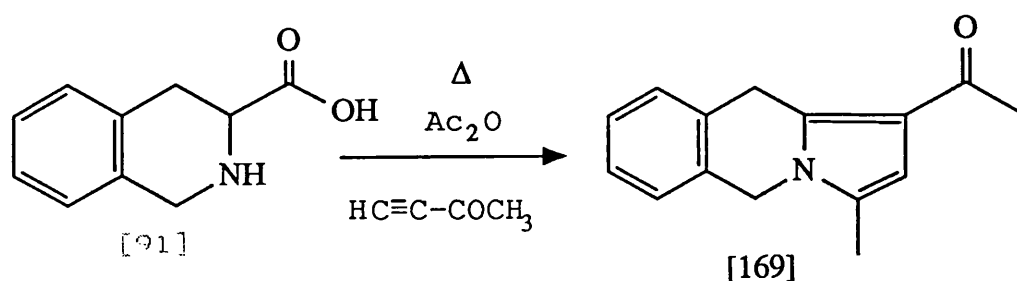
The dipolarophile ethyl phenyl propiolate proved more successful, as shown in figure 59. When it was added to a solution of the isoquinoline [91] in acetic anhydride and heated at 80°C for 8h, the dihydropyrroloisoquinoline [168] was isolated in 56% yield.

Figure 59.



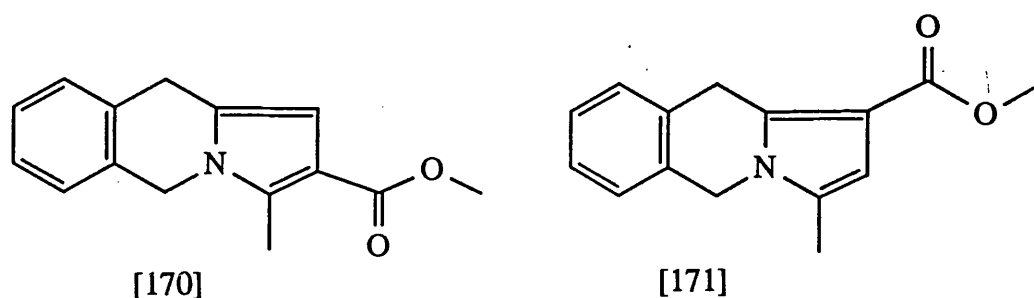
Similarly, heating 3-butyn-2-one in a solution of the isoquinoline in acetic anhydride resulted in successful 1,3-dipolar cycloaddition, giving the adduct [169] in 71% yield, as shown in figure 60. The conditions needed to effect the reaction in this case were more severe. Thus the temperature had to be raised to 130°C for 1.5h. The reasons for the difference in reactivity between the alkynic ketone and ester are not clear.

Figure 60.



These two reactions, in contrast to the cycloaddition performed using methyl propiolate as the dipolarophile, resulted in the isolation of only one isomer, in each case. The structural assignment of these products was made on the basis of ^1H N.M.R. data.

In the spectrum of [168], the resonance of the C-3 methyl protons occurs at δ 2.66. This is virtually the same position as the C-3 methyl protons in the adduct [170] and 0.37 ppm downfield relative to the same signal in the isomeric adduct [171].



Also, the C-9H₂ resonance of [168] occurs at δ 3.93, just 0.06 ppm upfield of the C-9H₂ resonance in [170], but 0.46 ppm upfield of the C-9H₂ resonance in [171].

In the ¹H N.M.R. spectrum of [169], the methine proton resonates as a quartet, spin-spin coupled (⁴J=0.9Hz) to the C- methyl protons at δ 2.39. Also, the C-9 methylene protons resonate at the relatively low field position of δ 4.44, which would be expected if the deshielding acetyl group was positioned at C-1.

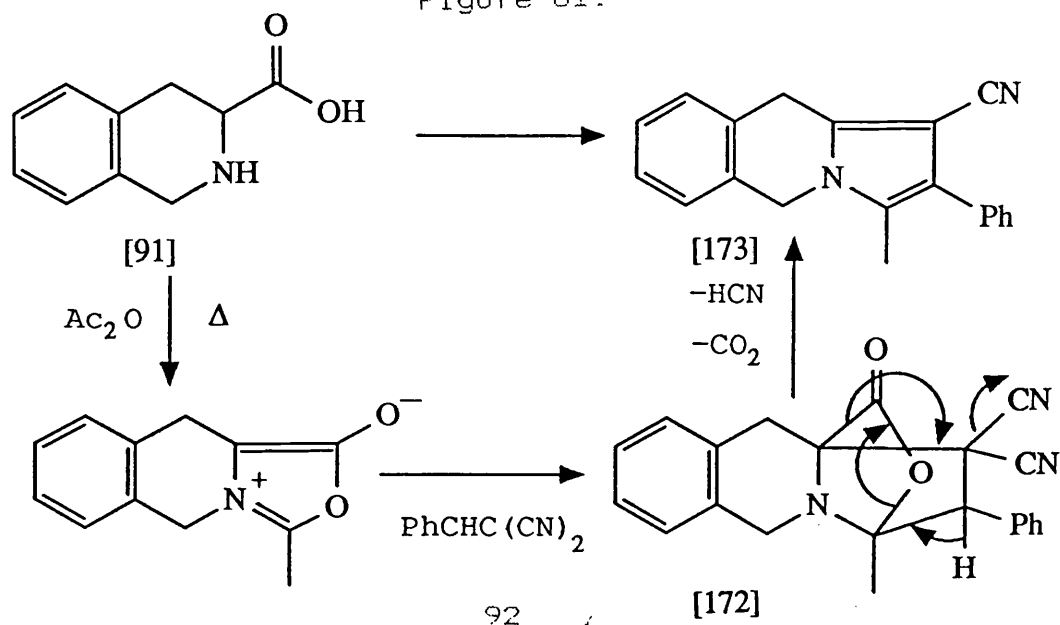
In order to further assess the range of dipolarophiles that might be used to form adducts with the munchnone, some potential heterodipolarophiles were used e.g. hexachloroacetone (C-O), methyl cyanide (C-N) and methyl cyanoacetate (C-N). In all cases these failed to give isolable adducts and the reaction mixtures became darker as time went by. We assume that this indicates the progressive degradation of the munchnone and it seems that these reagents are simply insufficiently reactive.

Other alkenyl dipolarophiles were also examined and these included dimethyl fumarate, dimethyl maleate, maleic anhydride and methyl methacrylate. Whilst possessing electron withdrawing groups and therefore having relatively lower energy LUMO's, which should facilitate reaction with the munchnone, these materials also failed to produce dihydropyrroloisoquinoline adducts.

Instead, t.l.c. analysis showed only the close running array of spots with which we associated the decomposition of the munchnone. Similar work by Hershen-son⁽¹⁷³⁾ on tetrahydro- β -carboline-3-carboxylic acids also resulted in mixtures of inseparable products.

The only alkenyl dipolarophile which proved successful in this type of intermolecular cyclization reaction was benzylidenemalononitrile, as shown in figure 61. When this was reacted with the isoquinoline [91], dissolved in acetic anhydride, and heated at reflux for 2h, the tricyclic adduct [173] was produced in 77% yield.

Figure 61.



Benzylidene malononitrile, unlike the previous alkenyl dipolarophiles, forms an initial adduct [172], which can increase its oxidation state by the elimination of hydrogen cyanide, hence facilitating the loss of carbon dioxide to form the dihydropyrroloisoquinoline [173]. This suggests that cycloadditions probably also occur with other alkenyl dipolarophiles such as dimethyl fumarate etc. but since the adducts cannot eliminate carbon dioxide they undergo retro addition and the molecule degrades.

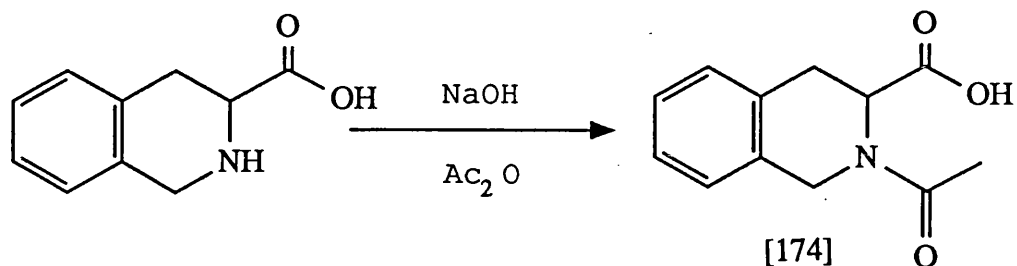
In these reactions, our supposition had always been that, first of all the isoquinoline reacted to form an amide, then an anhydride. At this point, one half of the anhydride acts as a leaving group (acetate anion) allowing the mesoionic oxazolium-5-olate to form. In an attempt to justify this conclusion, it was decided to perform some of these reactions in a stepwise manner, isolating the intermediates as they were formed.

Unfortunately at the temperature needed to initiate reaction between the isoquinoline [91] and acetic anhydride, 80°C, inseparable mixtures of products were obtained.

It was decided instead to use milder methods to generate the amide. Thus the isoquinoline [91] was treated with aqueous sodium hydroxide and acetic anhydride at

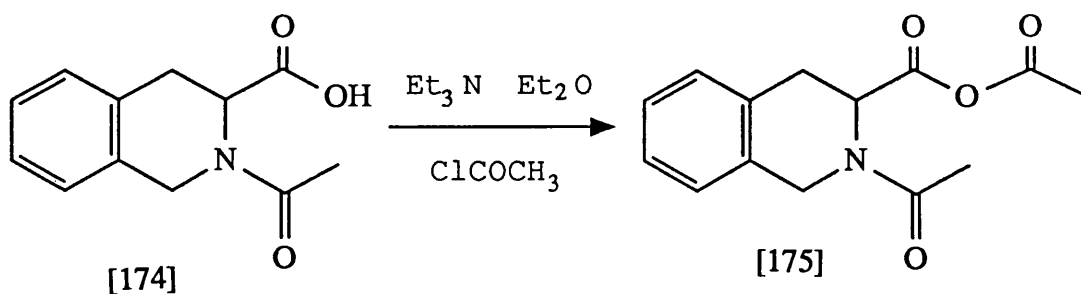
room temperature, as shown in figure 62. After work up, the amide [174] was obtained as a white solid in 93% yield.

Figure 62.



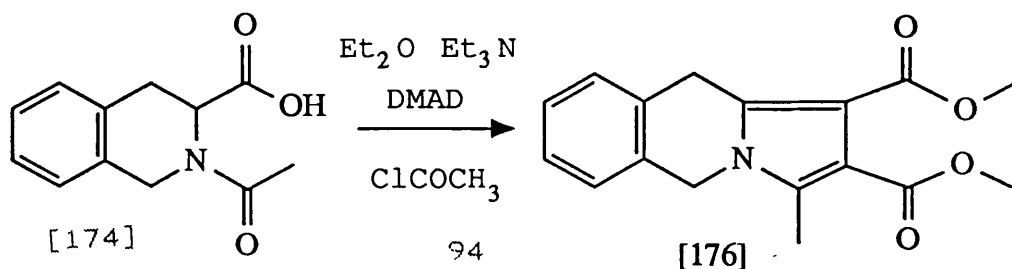
To form the mixed anhydride [175], the amide was added to a solution of triethylamine in ether. Acetyl chloride was then added to the acid salt. Unfortunately, the anhydride was not obtained, instead a multicomponent mixture was obtained.

Figure 63.



However, when this experiment was performed in the presence of dimethyl acetylenedicarboxylate at room temperature, shown in figure 64, the expected dihydropyrroloisoquinoline [176] was indeed formed in 71% yield.

Figure 64.



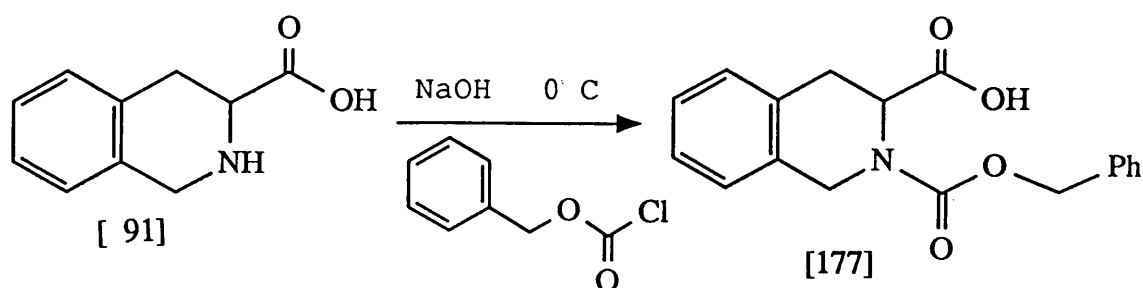
Thus we are unable to prove that the reaction progressed through a compound of type [175], or whether the oxazolium-5-olate was formed through straight dehydration of the isoquinoline with the acid group still present. Acids are not renowned for their electrophilicity however, so we still feel inclined to believe that prior activation is necessary.

It was not unexpected that the actual oxazolium-5-olate system could not be isolated as Huisgen⁽¹⁷⁴⁾ has shown this system to be highly reactive, although isolation has been possible when aromatic substituents are present at the 2 and 4 positions of the oxazolium-5-olate ring.

To round off the work, some reactions were performed to investigate the effect on the cycloaddition reaction of having groups other than an amido unit incorporated into the isoquinoline [91]

Hence, the carbamate [177], in figure 65, was produced in 58% yield by dissolving the isoquinoline [91] in aqueous sodium hydroxide and then adding benzyl chloroformate dropwise at 0°C.

Figure 65.

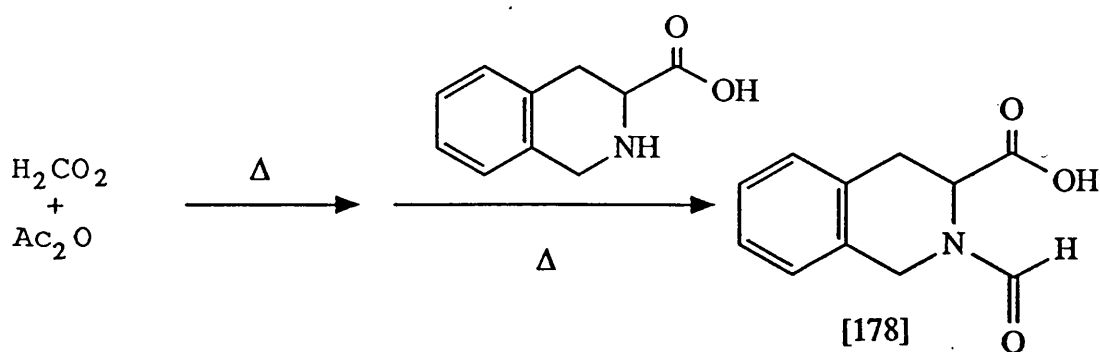


However, when heated in acetic anhydride in the presence of dimethyl acetylenedicarboxylate, this reactant failed to yield an adduct and upon work up only starting material was recovered. It seems probable that in carbamates, there is less electron density at the carbonyl oxygen atom than in amides and this is enough to inhibit the reaction.

It was also decided to form the N-formyl compound [178], shown in figure 66, to see if the munchnone formation depended upon the presence of an acetyl unit at the N-atom of the isoquinoline. Our expectation was that it should not since an alkyl C-group, adjacent to the carbonyl group would exert a relatively minor effect upon the electron density of the carbon atom.

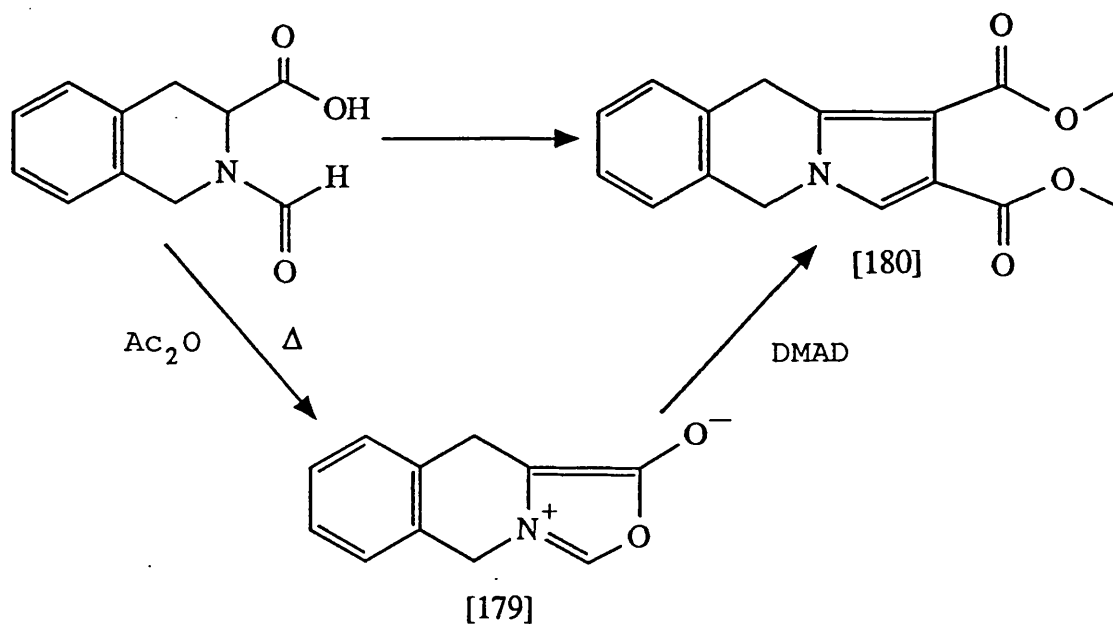
This proved correct, thus formic acid and acetic anhydride were heated at 60°C for 1h to form the mixed anhydride. The isoquinoline acid [91] was added to the reaction mixture and after a further 1h at 60°C, work up gave the amide [178] in 26% yield.

Figure 66.



This amide was then dissolved in acetic anhydride containing dimethyl acetylenedicarboxylate and after heating at 70°C for 1h an addition occurred to give a 54% yield of the desired dihydroisoquinoline [180].

Figure 67.



Experimental.

All solvents were dried and distilled before use. Petrol refers to petroleum ether of 60-80°C boiling range and ether to diethyl ether. T.l.c. was performed on aluminium plates coated with kieselgel 60F₂₅₄ (Merck 5554) and compounds were visualised by illumination with short wavelength U.V. light or by treatment with one of the following: iodine solution in petrol, aqueous potassium permanganate solution, phosphomolybdic acid solution in methanol or an alcoholic solution of vanillin. Column chromatography was performed on Amicon Matrex silica.

N.m.r spectra were recorded at 270MHz (¹H) using TMS as an internal standard.

All melting points are uncorrected.

Reagent used for chemical ionization (C.I.) is isobutane.

Where two methods were employed to synthesize a product, the analytical details are not repeated for method B, but are identical to those listed for method A.

3-Quinolinecarbonitrile [47].

To a solution of 3-bromoquinoline (3g, 14.4 mmol) in N-methyl-2-pyrrolidone (25 cm³) was added copper(I)cyanide (4.5g, 50 mmol). The solution was refluxed for 40 minutes. Dichloromethane (150 cm³) was then added and the solution extracted with dilute hydrochloric acid (4 x 100 cm³). The combined acidic portions were then basified with dilute ammonium hydroxide and extracted with dichloromethane (4 x 100 cm³). The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9) to yield the title compound as a white solid (391 mg, 18%); m.p.=103°C (lit.¹⁷⁵ 108-110°C) ν_{\max} (liquid film) cm⁻¹, 3040 (C-H), 1620 (C=C), 750 (C-H) ; δ_{H} (CDCl₃) ppm 9.02 (1H, d, ⁴J=2.0 Hz, CH=N), 8.53 (1H, d, ⁴J=2.0 Hz, CH=C-CN), 8.16 (1H, d, ³J=8.2 Hz, CH=C-N), 7.88 (2H, m, CH=CH-CH), 7.70 (1H, d, ³J=8.2 Hz, CH-CH=CH); m/z (E.I.) 154 (M⁺, 100%), 127 (24%).

1,2,3,4-Tetrahydroisoquinolinium-3-carboxylic acid chloride [66].

A suspension of phenylalanine (25g, 150 mmol) in a mixture of conc. hydrochloric acid (190 cm³) and 37%

formaldehyde solution (55cm³) was heated to reflux for 30 minutes, then a further quantity of conc. hydrochloric acid (50 cm³) and 37% formaldehyde solution (25 cm³) was added. Reflux was continued for 3h. The mixture was cooled and the colourless precipitate was collected by filtration, washed with methanol (3 x 100 cm³) and dried to yield the title compound (25.6g, 79%). M.p.= 305-307°C. (lit., 308-309°C (119))

Ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate [67]⁽¹⁷⁶⁾

A suspension of [66] (10g, 47 mmol) in absolute ethanol (400 cm³) was heated to reflux. Dry hydrogen chloride was passed through until the ethanol was saturated (5h.). The solvent was removed under vacuum and the residue was dissolved in the minimum volume of water and made alkaline with potassium carbonate. The yellow oil was separated and the aqueous solution was extracted with ether (3 x 50 cm³), the combined extracts were washed with water (2 x 20 cm³), and saline solution (2 x 20 cm³) and dried with sodium sulfate. This oil was distilled at reduced pressure to yield the title compound as a pale yellow oil (8.2g, 85%); ν_{\max} (liquid film) cm⁻¹, 3300 (N-H), 1705 (C=O), 755 (C-H); δ_{H} (CDCl₃) ppm 7.04 (4H, m, aromatic protons), 4.16 (2H, q, ³J=7.2 Hz, CH₂-CH₃), 4.00 (1H, d, ²J=15.7 Hz, CHH-NH), 3.96 (1H, d, ²J=15.7 Hz, CHH-NH), 3.60 (1H, dd, ³J=4.7 Hz, ³J=10.1 Hz, CH-CO₂Et), 2.98 (1H, dd, ³J=4.7 Hz, ²J=16.1 Hz, CHH-CH), 2.84 (1H,

dd, $^3J=10.1$ Hz, $^2J=16.1$ Hz, $\underline{\text{CHH}}\text{-CH}$), 2.20 (1H, s, N-H), 1.24 (3H, t, $^3J=7.2$ Hz, $\underline{\text{CH}}_3\text{-CH}_2$); m/z (C.I.) 206 (100%, MH^+), 132 $^+$ (85%).

Ethyl 2-(butan-1-oyl-4-ol)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate [68].

To a solution of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (410 mg, 2 mmol) in dichloromethane (5 cm^3) under an atmosphere of nitrogen at 0°C was added 2.0M trimethylaluminium in hexane (1 cm^3 , 2 mmol). The solution was allowed to warm to room temperature and stirring was continued for 4h. Gamma Butyrolactone (172 mg, 2 mmol) was then added and the mixture was stirred at room temperature for a further 12h. Ice water was added and the solution extracted with dichloromethane (3 \times 10 cm^3). The organic solution was then washed with water (3 \times 5 cm^3) and saturated sodium chloride solution (3 \times 5 cm^3) and dried with sodium sulfate. The solvent was removed under reduced pressure and the crude product purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:19 to 1:9) to yield the title product as a pale oil (30 mg, 5%); ν_{max} (liquid film) cm^{-1} 3615 (O-H), 3400-3200 (O-H), 1720 (C=O, ester), 1635 (C=O, amide); δ_{H} (CDCl_3) ppm (mixture of diastereoisomers) 7.22 (8H, m, aromatic protons), 5.45 (1H, dd, $^3J=3.5$ Hz, $\underline{\text{CH}}\text{-CH}_2$), 4.90 (1H, d, $^2J=17.2$ Hz, $\underline{\text{CHH}}\text{-N}$), 4.87 (1H, m, $\underline{\text{CH}}\text{-CH}_2$), 4.72 (2H, s, $\underline{\text{CH}}_2\text{-N}$), 4.56 (1H, d, $^2J=17.2$ Hz, $\underline{\text{CHH}}\text{-N}$), 4.06

(4H, m, 2 × $\text{CH}_2\text{-O-C=O}$), 3.74 (4H, m, 2 × $\text{CH}_2\text{-OH}$), 3.20 (4H, m, 2 × $\text{CH}_2\text{-CH}$), 2.69 (4H, m, 2 × $\text{CH}_2\text{-C=O}$), 2.22 (2H, br, 2 × O-H), 1.99 (4H, m, 2 × $\text{CH}_2\text{-CH}_2\text{-OH}$), 1.12 (3H, t, $^3J = 7.1$ Hz, $\text{CH}_3\text{-CH}_2$), 1.07 (3H, t, $^3J = 7.1$ Hz, $\text{CH}_3\text{-CH}_2$); m/z (C.I.) 292 (100%, MH⁺), 204 (68%), 132 (83%).

Ethyl 1,2,3,4-Tetrahydro-2-(ethan-1-oyl)-isoquinoline-3-carboxylate [73].

Method A.

A solution of acetic acid (0.058g, 0.97 mmol), 1,3-dicyclohexylcarbodiimide (0.2g, 0.97 mmol) and ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.1g, 0.48 mmol) in dichloromethane (10 cm³) was stirred together at room temperature for 15h. The 1,3-dicyclohexylurea was removed by filtration and the remaining solution was washed with sodium bicarbonate solution (2 × 5 cm³), dilute hydrochloric acid (2 × 5 cm³), water (2 × 5 cm³) and brine (2 × 5 cm³) and dried with sodium sulfate. The crude product was purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9) to yield the title compound as a yellow oil (52.4 mg, 44%); ν_{max} (liquid film) cm⁻¹ 2920-2810 (C-H), 1720 (C=O, ester), 1630 (C=O, amide); δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 7.21 (8H, m, aromatic protons), 5.47 (1H, dd, $^3J = 3.6$ Hz, $^3J = 6.1$ Hz, CH-CH_2), 4.89 (1H, d, $^2J = 17.1$ Hz, CH-HN), 4.77 (1H, dd, $^3J = 2.9$ Hz, $^3J = 5.6$ Hz, CH-CH_2),

4.73 (1H, d, $^2J=15.6$ Hz, $\underline{\text{CH}}\text{-HN}$), 4.67 (1H, d, $^2J=15.6$ Hz, $\underline{\text{CH}}\text{-HN}$), 4.54 (1H, d, $^2J=17.1$ Hz, $\underline{\text{CH}}\text{-HN}$), 4.06 (4H, m, $2 \times \underline{\text{CH}}_2\text{-O}$), 3.37-3.09 (4H, m, $2 \times \underline{\text{CH}}_2\text{-CH}$), 2.26 (3H, s, $\underline{\text{CH}}_3\text{-C=O}$), 2.16 (3H, s, $\underline{\text{CH}}_3\text{-C=O}$), 1.12 (3H, t, $^3J=7.0$ Hz, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$), 1.08 (3H, t, $^3J=7.0$ Hz, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); m/z (E.I) 247 (27%, M⁺), 204 (48%), 174 (25%), 132 (100%); C₁₄H₁₇NO₃ : Acc.Mass : Requires 247.29325, Found 247.29299.

Method B.

A solution of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.41g, 2 mmol), acetic acid (0.06g, 1 mmol) and boron trifluoride etherate (0.284g, 2 mmol) in toluene (30 cm³) under an atmosphere of nitrogen was refluxed in a Soxhlet apparatus with magnesium sulfate as the drying agent for 48h. The solution was then washed with 10% sodium hydroxide solution (2×10 cm³), dilute hydrochloric acid (2×10 cm³), water (2×10 cm³) and brine (2×10 cm³) and dried with sodium sulfate. The crude product was purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9) to yield the title compound as a pale yellow oil (20.6 mg, 8.3%).

Ethyl 1,2,3,4-tetrahydro-2-(hexan-1-oyl)isoquinoline-3-carboxylate. [74].

To a solution of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.42g, 6.9 mmol) and 1-hexanoic acid (0.8g, 6.9 mmol) in dichloromethane (15 cm³) was added 1,3-

dicyclohexylcarbodiimide (1.42g, 0.69 mmol). The solution was stirred at room temperature for 48h. The 1,3-dicyclohexylurea was then removed by filtration. The remaining solution was washed with dilute hydrochloric acid ($2 \times 5 \text{ cm}^3$) and dried with sodium sulfate. The solvent was removed under reduced pressure and the crude product purified by silica gel column chromatography (ethyl acetate : pet ether, 1:9 to 1:3) to yield the title compound as a clear oil (904.5 mg, 43%); ν_{max} (liquid film) cm^{-1} 2940-2810 (C-H), 1730 (C=O, ester), 1635 (C=O, amide); δ_{H} (CDCl_3) ppm (mixture of diastereoisomers) 7.22 (8H, m, aromatic protons), 5.48 (1H, dd, $^3J=5.9\text{Hz}$, $^3J=3.5\text{Hz}$, CH-CH_2), 4.92 (1H, d, $^2J=16.9 \text{ Hz}$, CHH-N), 4.83 (1H, dd, $^3J=3.1 \text{ Hz}$, $^3J=3.1 \text{ Hz}$, CH-CH_2), 4.70 (2H, s, $\text{CH}_2\text{-N}$), 4.53 (1H, d, $^2J=16.9 \text{ Hz}$, CHH-N), 4.06 (4H, m, $2 \times \text{CH}_2\text{-O}$), 3.22 (4H, m, $2 \times \text{CH}_2\text{-CH}$), 2.48 (4H, m, $2 \times \text{CH}_2\text{-C=O}$), 1.70 (4H, m, $2 \times \text{CH}_2\text{-CH}_2\text{-C=O}$), 1.37 (8H, m, $2 \times \text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.13 (3H, t, $^3J=7.2 \text{ Hz}$, $\text{CH}_3\text{-CH}_2\text{-O}$), 1.07 (3H, t, $^3J=7.2 \text{ Hz}$, $\text{CH}_3\text{-CH}_2\text{-O}$), 0.92 (6H, m, $2 \times \text{CH}_3\text{-CH}_2\text{-CH}_2$); m/z (E.I.) 303 (48%, M^+), 230 (76%), 204 (63%), 132 (100%); $\text{C}_{18}\text{H}_{25}\text{NO}_3$: Acc. Mass. : Requires 303.4004, Found 303.3942.

5,7,12,14-Tetrahydrodinaphth[*a,d*]-6,13-diketopiperazine [76].

The isoquinoline [67] (6.2g, 30 mmol) was heated to reflux with gamma-butyrolactone (3 cm^3 , 40 mmol) for

48h. During this time, the solution became orange in colour. Dilute hydrochloric acid was added and the organic layer separated. The remaining acidic layer was extracted with diethyl ether ($2 \times 20 \text{ cm}^3$). The extracts were combined, washed with water ($2 \times 10 \text{ cm}^3$) and saline solution ($2 \times 10 \text{ cm}^3$) and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : pet. ether, 1:1). The solid was dissolved in the minimum amount of boiling ethyl acetate and allowed to crystallize to yield the title compound as a tan solid (1.76g, 37%); ν_{max} (CHCl_3) cm^{-1} 2870-2820 (C-H), 1625 (C=O); δ_{H} (CDCl_3) ppm 7.24 (8H, m, aromatic protons), 5.40 (2H, d, $^2J=17.2 \text{ Hz}$, $2 \times \text{CHH-N}$), 4.36 (2H, d, $^2J=17.2 \text{ Hz}$, $2 \times \text{CHH-N}$), 4.30 (2H, dd, $^3J=3.8 \text{ Hz}$, $^3J=11.9 \text{ Hz}$, $2 \times \text{CH-CH}_2$), 3.46 (2H, dd, $^3J=3.8 \text{ Hz}$, $^2J=16.0 \text{ Hz}$, $2 \times \text{CHH-CH}$), 3.02 (2H, dd, $^3J=11.9 \text{ Hz}$, $^2J=16.0 \text{ Hz}$, $2 \times \text{CHH-CH}$); m/z (E.I) 318 (100%, M^+), 130 (57%), 104 (65%); $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2$: Acc.Mass : Requires 318.13683, Found 318.13659.

Ethyl 1,2,3,4-tetrahydro-2-(5-bromopentan-1-oyl)-isoquinoline-3-carboxylate [78].

To a solution of 5-bromopentanoic acid (0.9g, 5 mmol) and cyanuric chloride (0.46g, 2.5 mmol) in acetone (10 cm^3) was added triethylamine (0.7 cm^3 , 5 mmol). This was stirred for 3h at 30°C , at which time no more cyanuric

chloride was present in solution. The isoquinoline [67] (1.03g, 5mmol) and sodium carbonate (0.53g, 5 mmol) were then added and stirring continued at 30°C for 2h. The triazine derivative was then filtered off. The acetone was removed under vacuum and the orange oil taken up in dichloromethane (50 cm³) and washed with dilute hydrochloric acid (2 x 30 cm³), dilute sodium hydroxide (2 x 10 cm³) and water (2 x 10 cm³). The solution was dried with sodium sulfate, then the solvent was removed and the product distilled under reduced pressure to yield the title compound as a clear oil (1.5g, 82%); ν_{\max} (liquid film) cm⁻¹ 2910-2820 (C-H), 1720 (C=O, ester), 1620 (C=O, amide); δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 7.26 (8H, m, aromatic protons), 5.44 (1H, dd, ³J=4.0 Hz, ³J=6.2 Hz, CH-CH₂), 4.89 (1H, d, ²J=16.1 Hz, CHH-N), 4.81 (1H, dd, ³J=3.9 Hz, ³J=6.0 Hz, CH-CH₂), 4.69 (2H, s, CH₂-N), 4.53 (1H, d, ²J=16.1 Hz, CHH-N), 4.06 (2H, q, ³J=7.0 Hz, CH₂-CH₃), 4.05 (2H, q, ³J=7.3 Hz, CH₂-CH₃), 3.45 (2H, t, ³J=6.6Hz, CH₂-Br), 3.42 (2H, t, ³J=4.8Hz, CH₂Br), 3.25 (4H, m, 2 x CH₂-CH), 2.53 (4H, m, 2 x CH₂-CO), 1.88 (8H, m, 2 x CH₂-CH₂-CH₂-Br), 1.12 (3H, t, ³J=7.0 Hz, CH₃-CH₂), 1.07 (3H, t, ³J=7.3 Hz, CH₃-CH₂); m/z (C.I) 368 (15%, M+), 288 (10%), 204 (90%), 132 (100%).

Methyl 4-Bromobutanoate [83]⁽¹⁷⁷⁾

A solution of gamma butyrolactone (0.75 cm³, 10 mmol) in dichloromethane (10 cm³) was added to a solution of 1M

boron tribromide in dichloromethane (1 cm^3 , 10 mmol) under nitrogen. The solution was then quenched after 14h by the slow addition of methanol (30 cm^3). Dichloromethane (50 cm^3) was then added and the solution washed with saturated sodium hydrogen carbonate solution ($2 \times 25\text{ cm}^3$), saturated sodium thiosulphate solution ($2 \times 25\text{ cm}^3$), and water ($2 \times 25\text{ cm}^3$) and dried with sodium sulfate. The solvent was removed and the crude product distilled under reduced pressure to yield the title compound as an orange oil (0.96g, 53%); ν_{max} (liquid film) cm^{-1} 1735 (C=O), 760 (C-Br); δ_{H} (CDCl_3) ppm 3.70 (3H, s, $\text{CH}_3\text{-O}$), 3.48 (2H, t, $^3J=6.4\text{ Hz}$, $\text{CH}_2\text{-Br}$), 2.52 (2H, t, $^3J=7.2\text{ Hz}$, $\text{CH}_2\text{-CO}$), 2.18 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CO}$); m/z (C.I.) 151 (33%), 149 (37%), 101 (100%), 87 (94%).

Ethyl 4-bromobutanoate [84]⁽¹³²⁾

A solution of gamma-butyrolactone (1.5 cm^3 , 20 mmol) in absolute ethanol (5 cm^3) was rapidly stirred at 0°C while dry hydrogen bromide gas (4.05g, 50 mmol) was slowly bubbled through. The solution was stirred for a further 2 h. at 0°C . 10g of ice was added and the aqueous mixture was extracted with diethyl ether ($3 \times 10\text{ cm}^3$). The ether solution was washed with saturated sodium hydrogen carbonate solution ($2 \times 10\text{ cm}^3$), sodium thiosulfate solution ($2 \times 10\text{ cm}^3$), water ($2 \times 10\text{ cm}^3$) and saline solution ($2 \times 10\text{ cm}^3$) and dried with sodium sulfate. The solvent was removed and the crude product was distilled under reduced

pressure to yield the title compound as a pale yellow oil (3.23g, 83%); ν_{\max} (liquid film) cm^{-1} 2950 (C-H), 1720 (C=O), 770 (C-Br); δ_{H} (CDCl_3) ppm. 4.14 (2H, q, $^3J=7.2$ Hz, $\text{CH}_2\text{-CH}_3$), 3.47 (2H, t, $^3J=6.5$ Hz, $\text{CH}_2\text{-Br}$), 2.50 (2H, t, $^3J=7.2$ Hz, $\text{CH}_2\text{-CO}$), 2.18 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 1.27 (3H, t, $^3J=7.2$ Hz, $\text{CH}_3\text{-CH}_2$); m/z (C.I.) 197 (75%, MH^+), 195 (68%, MH^+), 149 (40%), 115 (40%).

6-Decynoic acid [85]⁽¹⁷⁸⁾

To a stirred solution of 1-pentyne (1 cm^3 , 10 mmol), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.2 cm^3 , 10 mmol) and tetrahydrofuran (10 cm^3) at -78°C , a solution of 1.6M butyllithium in hexane (9.38 cm^3 , 15 mmol) was added dropwise. The solution was kept at -78°C for a further 1h., then 5-bromopentanoic acid (0.9g, 5 mmol) was added. The solution was then immersed in a sonic bath for 2.5 h., before being quenched with saturated ammonium chloride solution (5 cm^3). Dilute hydrochloric acid (5 cm^3) was added and the solution was extracted with diethyl ether (2 \times 20 cm^3), washed with water (2 \times 10 cm^3), and saline solution (2 \times 10 cm^3) and dried with sodium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:3) to yield the title compound as a pale yellow oil (0.29g, 35%); ν_{\max} (liquid film) cm^{-1} 3100 (O-H), 2900 (C-H), 1690 (C=O); δ_{H} (CDCl_3) ppm 10.8 (1H, br, COOH), 2.39 (2H, t, $^3J=7.1$ Hz, $\text{CH}_2\text{-CO}$),

2.19 (2H, m, $\text{CH}_2\text{-C}\equiv\text{C}$), 2.12 (2H, m, $\text{CH}_2\text{-C}\equiv\text{C}$), 1.75 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CO}_2\text{H}$), 1.51 (4H, m, $2 \times \text{CH}_2\text{-CH}_2\text{-C}\equiv\text{C}$), 0.97 (3H, t, $^3\text{J}=7.1$ Hz, $\text{CH}_3\text{-CH}_2$); m/z (C.I.) 169 (24%, MH^+), 151 (100%), 67 (78%).

5-Nonynoic acid [86]⁽¹⁷⁹⁾

To a stirred solution of 1-pentyne (1 cm³, 10 mmol), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.2 cm³, 10 mmol) and tetrahydrofuran (10 cm³) at -78°C, a solution of 1.6M butyllithium in hexane (9.38 cm³, 15 mmol) was added dropwise. The solution was kept at -78°C for a further 1h., then 4-bromobutanoic acid (0.84g, 5 mmol) was added. The solution was then immersed in a sonic bath for 2h., before being quenched with saturated ammonium chloride solution (5 cm³). Dilute hydrochloric acid (5cm³) was added and the solution was extracted with diethyl ether (2 x 20 cm³), washed with water (2 x 10 cm³), and saline solution (2 x 10 cm³) and dried with sodium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:3) to yield the title compound as a pale yellow oil (0.24g, 31%); ν_{max} (liquid film) cm⁻¹ 3200 (C-H), 2900 (C-H), 1685 (C=O); δ_{H} (CDCl₃) ppm 10.77 (1H, br, COOH), 2.42 (2H, t, $^3\text{J}=7.1$ Hz, $\text{CH}_2\text{-CO}$), 2.22 (2H, m, $\text{CH}_2\text{-C}\equiv\text{C}$), 2.13 (2H, m, $\text{CH}_2\text{-C}\equiv\text{C}$), 1.77 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CO}_2\text{H}$), 1.51 (2H, m, $\text{CH}_2\text{-CH}_2\text{-C}\equiv\text{C}$), 0.97 (3H, t, $^3\text{J}=7.1$ Hz, $\text{CH}_3\text{-CH}_2$); m/z (C.I.)

155 (32%, MH⁺), 137 (100%), 87 (22%), 67 (85%).

Ethyl 1,2,3,4-tetrahydro-2-(dec-6-yn-1-oyl)-
isoquinoline-3-carboxylate [87].

To a solution of 6-decynoic acid (0.5g, 3 mmol) and cyanuric chloride (0.28g, 1.5 mmol) in dry acetone (10 cm³) was added triethylamine (0.4 cm³, 3 mmol). The solution was warmed at 40°C for 2h. when t.l.c. indicated the disappearance of cyanuric chloride. The isoquinoline [67] (0.62g, 3 mmol) and sodium carbonate (0.31g, 3 mmol) were then added and the solution stirred for a further 3h. at 34°C. The triazine precipitate was removed by filtration. The acetone was removed under reduced pressure. The remaining oil was taken up in a mixture of diethyl ether (45 cm³) and dichloromethane (5 cm³) and washed with dilute hydrochloric acid (2 x 25 cm³), dilute sodium hydroxide (2 x 15 cm³), and water (2 x 15 cm³) and dried with sodium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9 to 1:2) to yield the title compound as a clear yellow oil (0.85g, 75%); ν_{\max} (liquid film) cm⁻¹ 2880-2820 (C-H), 1720 (C=O, ester), 1625 (C=O, amide); δ_H (CDCl₃) ppm (mixture of diastereoisomers) 7.20 (8H, m, aromatic protons), 5.47 (1H, dd, ³J=3.6 Hz, ³J=6.0 Hz, CH-CH₂), 4.92 (1H, d, ²J=17.4 Hz, CHH-N), 4.83 (1H, dd, ³J=3.1 Hz, ³J=5.5 Hz, CH-CH₂), 4.70 (2H, s, CH₂-N), 4.53 (1H, d,

$^2J=17.4$ Hz, $\underline{\text{CHH}}\text{-N}$), 4.06 (4H, m, $2 \times \underline{\text{CH}}_2\text{-CH}_3$), 3.22 (4H, m, $2 \times \underline{\text{CH}}_2\text{-CH}$), 2.52 (2H, t, $^3J=7.8$ Hz, $\underline{\text{CH}}_2\text{-CO}$), 2.51 (2H, t, $^3J=7.7$ Hz, $\underline{\text{CH}}_2\text{-CO}$), 2.22 (4H, m, $2 \times \underline{\text{CH}}_2\text{-C}\equiv\text{C}$), 2.11 (4H, m, $2 \times \underline{\text{CH}}_2\text{-C}\equiv\text{C}$), 1.81 (4H, m, $2 \times \underline{\text{CH}}_2\text{-CH}_2\text{-CO}$), 1.53 (8H, m, $4 \times \underline{\text{CH}}_2\text{-CH}_2\text{-C}\equiv\text{C}$), 1.13 (3H, t, $^3J=7.1$ Hz, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$), 1.07 (3H, t, $^3J=7.1$ Hz, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$), 0.96 (3H, t, $^3J=7.3$ Hz, $\underline{\text{CH}}_3\text{-CH}_2\text{-CH}_2$), 0.95 (3H, t, $^3J=7.3$ Hz, $\underline{\text{CH}}_3\text{-CH}_2\text{-CH}_2$); m/z (C.I.) 356 (100%, MH⁺), 288 (31%), 204 (82%), 132 (66%), 130 (29%).

1,2,3,4-Tetrahydro-2-(dec-6-yn-1-oyl)-isoquinoline-3-carboxylic acid [89].

Method A.

The isoquinoline [87] (99 mg, 0.28 mmol), 1,4,7,10,13,16-hexaoxacyclooctadecane (22 mg, 0.084 mmol) and potassium superoxide (60 mg, 0.84 mmol) were added to dry benzene (5 cm³). The solution was stirred at room temperature overnight. Water (5 cm³) and dilute hydrochloric acid were added until the solution was acidic. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 20 cm³). The organic portions were combined and extracted with dilute sodium bicarbonate solution (3 x 20 cm³). These extracts were acidified with dilute hydrochloric acid and the solution was then extracted with diethyl ether (3 x 20 cm³). The organic layer was washed with water (2 x 10 cm³) and saline

solution ($2 \times 10 \text{ cm}^3$) and dried with sodium sulfate. The solvent was removed and the oil was distilled under reduced pressure to yield the title compound as a pale yellow oil (70 mg, 77%). ν_{max} (liquid film) cm^{-1} 2890-2830 (C-H), 1720 (C=O, ester), 1630 (C=O, amide); δ_{H} (CDCl_3) ppm (mixture of diastereoisomers) 7.22 (8H, m, aromatic protons), 5.40 (1H, dd, $^3J=4.4 \text{ Hz}$, $^3J=6.5 \text{ Hz}$, $\text{CH}-\text{CH}_2$), 5.80 (2H, br, $2 \times \text{O}-\text{H}$) 4.94 (1H, d, $^2J=17.6 \text{ Hz}$, $\text{CHH}-\text{N}$), 4.86 (1H, dd, $^3J=2.6 \text{ Hz}$, $^3J=5.1 \text{ Hz}$, $\text{CH}-\text{CH}_2$), 4.68 (1H, d, $^2J=16.4 \text{ Hz}$, $\text{CHH}-\text{N}$), 4.64 (1H, d, $^2J=16.4 \text{ Hz}$, $\text{CHH}-\text{N}$), 4.49 (1H, d, $^2J=17.6 \text{ Hz}$, $\text{CHH}-\text{N}$), 3.25 (4H, m, $2 \times \text{CH}_2-\text{CH}$), 2.51 (2H, t, $^3J=7.6 \text{ Hz}$, CH_2-CO), 2.50 (2H, t, $^3J=7.5 \text{ Hz}$, CH_2-CO), 2.21 (4H, m, $2 \times \text{CH}_2-\text{C}\equiv\text{C}$), 2.11 (4H, m, $2 \times \text{CH}_2-\text{C}\equiv\text{C}$), 1.80 (4H, m, $2 \times \text{CH}_2-\text{CH}_2-\text{CO}$), 1.50 (8H, m, $4 \times \text{CH}_2-\text{CH}_2-\text{C}\equiv\text{C}$), 0.95 (6H, t, $^3J=7.3 \text{ Hz}$, $2 \times \text{CH}_3-\text{CH}_2$); m/z (C.I.) 328 (46%, MH^+), 260 (27%), 176 (45%), 151 (42%), 132 (60%), 109 (100%).

Method B.

The isoquinoline [87] (99 mg, 0.28 mmol) and sodium hydroxide (13 mg, 0.33 mmol) were dissolved in a solution of tetrahydrofuran (5 cm^3) and water (5 cm^3). The solution was stirred at room temperature for 12h. Dilute hydrochloric acid was added until the solution was acidic. The organic layer was separated and the remaining aqueous layer was extracted with diethyl ether ($2 \times 20 \text{ cm}^3$). The organic portions were combined and extracted

with dilute sodium bicarbonate solution ($3 \times 20 \text{ cm}^3$). This solution was made acidic with dilute hydrochloric acid and then extracted with diethyl ether ($3 \times 20 \text{ cm}^3$), washed with water ($2 \times 10 \text{ cm}^3$) and saline solution ($2 \times 10 \text{ cm}^3$) and dried with sodium sulfate. The solvent was removed and the crude product distilled under reduced pressure to yield the title compound as a light yellow oil (72 mg, 79%).

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [91]⁽¹⁷⁶⁾

The isoquinoline [66] (10 g, 47 mmol) was dissolved in a minimum volume of ethanol/water (2:1) and neutralised to congo red with 2N ammonium hydroxide. The resulting solution was left to crystallize overnight. The resulting solid was filtered off, washed with water ($3 \times 50 \text{ cm}^3$) and dried to yield the title compound as colourless, platelike crystals (8.3 g, 100%). $\text{C}_{10}\text{H}_{11}\text{NO}_2$: Acc.Mass.: Calculated 177.07898, Found 177.07763.

Dimethyl 4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline-1,2-dicarboxylate [92].

Method A.

The isoquinoline [91] (88 mg, 0.5 mmol) was added to acetic anhydride (10 cm^3) and dimethyl acetylenedicarboxylate (170 mg, 1.2 mmol). The mixture was stirred and

heated at 80°C for 12h. The solvent was removed under reduced pressure to yield a tan solid. This was dissolved in hot ethanol and left to crystallize, to yield the title compound as colourless crystals (95 mg, 63%). ν_{\max} (CHCl₃) cm⁻¹ 2920-2900 (C-H), 1670 (C=O) ; δ_{H} (CDCl₃) ppm 7.28 (4H, m, aromatic protons), 4.95 (2H, s, CH₂-N), 4.30 (2H, s, CH₂-C=C), 3.85 (6H, s, 2 x CH₃-O), 2.46 (3H, s, CH₃-C=C); m/z (E.I.) 299 (50%, M+), 268 (100%), 240 (16%), 141 (18%) ; C₁₇H₁₇NO₄ Found : C, 68.1; H, 5.8; N, 4.9: Requires : C, 68.2; H, 5.7; N, 4.7%.

Method B.

To a solution of the isoquinoline amide [174] (35 mg, 0.159 mmol), triethylamine (19 mg, 0.159 mmol) and dimethyl acetylenedicarboxylate (34 mg, 0.239 mmol) in diethyl ether (20 cm³), stirred under an atmosphere of nitrogen at room temperature was added acetyl chloride (12.5 mg, 0.159 mmol). The solution was stirred for 1h. Ethyl acetate (30 cm³) was then added and the solution washed with dilute hydrochloric acid (3 x 20 cm³), saturated sodium hydrogen carbonate solution (2 x 20 cm³), water (2 x 20 cm³) and saturated saline solution (2 x 20 cm³) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue dissolved in hot ethanol. The title compound was obtained as colourless crystals (34 mg, 71%).

Methyl 4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline-1-carboxylate and Methyl 4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline-2-carboxylate [93] and [94].

The isoquinoline [91] (88 mg, 0.5 mmol) was added to acetic anhydride (10 cm³) and methyl propiolate (100 mg, 1.2 mmol). The mixture was stirred and heated at 100°C for 2h. The solvent was removed under reduced pressure and the remaining yellow oil was purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9 to 1:3). This yielded the title compound as a pale yellow oil (89 mg, 74%); ν_{\max} (liquid film) cm⁻¹ 2930-2900 (C-H), 1670 (C=O) ; δ_{H} (CDCl₃) ppm (mixture of regioisomers) 7.25 (8H, m, aromatic protons), 6.33 (1H, t, ⁴J=1.0 Hz, CH=C-CH₂), 6.31 (1H, q, ⁴J=0.9 Hz, CH=C-CH₂), 4.93 (2H, br, s, CH₂-N), 4.92 (2H, br, s, CH₂-N), 4.39 (2H, br, s, CH₂-C=C-C=O), 3.99 (2H, d, ⁴J=1.0 Hz, CH₂-C=C-CH), 3.81 (3H, s, CH₃-O), 3.79 (3H, s, CH₃-O), 2.61 (3H, s, CH₃-C=C-C=O), 2.29 (3H, d, ⁴J=0.9 Hz, CH₂-C=C-CH); m/z (E.I.) 241 (100%, M+), 226 (92%), 210 (36%), 182 (84%).

1,2,3,4-Tetrahydro-2-(oct-1-oyl- ϵ -yn-8-oic acid)
isoquinoline-3-carboxylic acid [96].

The isoquinoline [107] (0.1g, 0.27 mmol) and sodium hydroxide (25.9 mg, 0.65 mmol) were dissolved in a solution of tetrahydrofuran (5 cm³) and water (5 cm³) and stirred at room temperature for 1h. The solvent was

removed under reduced pressure and the solution was made acidic with dilute hydrochloric acid. This was extracted with diethyl ether ($2 \times 10 \text{ cm}^3$). The organic portions were combined and extracted with sodium carbonate solution ($3 \times 10 \text{ cm}^3$). These extracts were acidified with dilute hydrochloric acid and extracted with diethyl ether ($3 \times 10 \text{ cm}^3$). The combined organic portions were washed with water ($2 \times 5 \text{ cm}^3$) and saline solution ($2 \times 5 \text{ cm}^3$) and dried with magnesium sulfate. The solvent was removed and the product distilled under reduced pressure to yield the title compound as a clear oil (81 mg, 91%); v_{max} (CHBr_3) cm^{-1} 2953-2852 (C-H), 2900 (br, O-H), 2235 ($\text{C}\equiv\text{C}$), 1713 ($\text{C}=\text{O}$, acid), 1640 ($\text{C}=\text{O}$, amide); δ_{H} (CDCl_3) ppm (mixture of diastereoisomers) 7.10 (8H, m, aromatic protons), 7.01 (4H, br, 4 \times O-H), 5.33 (1H, dd, $^3J=6.2$ Hz, $^3J=4.2$ Hz, $\text{CH}-\text{CH}_2$), 4.87 (1H, d, $^2J=17.6$ Hz, $\text{CHH}-\text{N}$), 4.82 (1H, m, $\text{CH}-\text{CH}_2$), 4.63 (2H, s, CH_2-N), 4.48 (1H, d, $^2J=17.6$ Hz, $\text{CHH}-\text{N}$), 3.15 (4H, m, 2 \times CH_2-CH), 2.52 (4H, m, 2 \times CH_2-CO), 2.35 (4H, m, 2 \times $\text{CH}_2-\text{C}\equiv\text{C}$), 1.70 (8H, m, 2 \times $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{O}$); m/z (F.A.B) 330 (100%, MH^+), 312 (20%), 284 (15%), 232 (20%), 176 (32%).

1-(*t*-Butyldimethylsiloxy)-5-chloropentane [101]⁽¹⁸⁰⁾

5-Chloropentanol (1 g, 8.2 mmol), 1-(*t*-butyldimethylsilyl)imidazole (1.9 g, 10.6 mmol) and dry dichloromethane (10 cm^3) were stirred at room temperature for 18h. The mixture was then added to dichloromethane (75 cm^3)

and washed with dilute hydrochloric acid ($3 \times 50 \text{ cm}^3$), dilute sodium bicarbonate solution ($3 \times 50 \text{ cm}^3$) and saline solution ($2 \times 50 \text{ cm}^3$). The solvent was removed and the residue distilled under reduced pressure to yield the title compound as a clear oil (1.9 g, 100%); ν_{max} (nujol) cm^{-1} 2954-2857 (C-H), 1255 ($\text{CH}_3\text{-Si}$), 1106 (Si-O-C), 835 (Si-O-C), 776 (C-Cl); δ_{H} (CDCl_3) ppm 3.57 (2H, t, $^3J=7.0$ Hz, $\text{CH}_2\text{-O}$), 3.49 (2H, t, $^3J=7.2$ Hz, $\text{CH}_2\text{-Cl}$), 1.75 (2H, m, $^3J=7.2$ Hz, $\text{CH}_2\text{-CH}_2\text{-O}$), 1.46 (4H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-Cl}$), 0.84 (9H, s, $3 \times \text{CH}_3\text{-C-Si}$), 0.01 (6H, s, $2 \times \text{CH}_3\text{-Si}$); m/z (C.I) 327 (64%, MH+), 179 (10%), 123 (19%), 105 (10%), 93 (14%), 86 (9%), 69 (100%).

7-(*t*-Butyldimethylsiloxy)hept-1-yne [102].

To a solution of the iodide [100] (0.4 g, 1.2 mmol) in dimethylformamide (1 cm^3) under an atmosphere of nitrogen, was added 18% sodium acetylide in xylene (0.6 g, 2.4 mmol). The solution was stirred at room temperature for 15h. Ice (10 g) was added and the solution was extracted with diethyl ether ($3 \times 10 \text{ cm}^3$). The organic portions were washed with water ($2 \times 5 \text{ cm}^3$) and saline solution ($2 \times 5 \text{ cm}^3$) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:49) to yield the title compound as an orange oil (0.17 g, 63%); ν_{max} (CHBr_3) cm^{-1} 3301 ($\equiv\text{C-H}$), 2952-2854 (C-H), 1255 (Si- CH_3), 1091 (Si-O-C), 835

(Si-O-C); δ_H (CDCl₃) ppm 3.56 (2H, t, $^3J=7.0$ Hz, $\text{CH}_2\text{-O}$), 2.15 (2H, td, $^3J=7.0$ Hz, $^4J=2.3$ Hz, $\text{CH}_2\text{-C}\equiv\text{C}$), 1.88 (1H, t, $^4J=2.3$ Hz, $\text{CH-C}\equiv\text{C}$), 1.48 (6H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-O}$), 0.84 (9H, s, 3 \times $\text{CH}_3\text{-C}$), 0.01 (6H, s, 2 \times $\text{CH}_3\text{-Si}$); m/z (C.I.) 201 (85%), 95 (30%), 81 (26%).

Methyl 8-(t-butyldimethylsiloxy)oct-2-ynoate [103]⁽¹⁸¹⁾

To a solution of the alkyne [102] (88 mg, 0.39 mmol) in dry tetrahydrofuran (1 cm³) at -78°C under an atmosphere of nitrogen was added 1.6M butyllithium (0.27 cm³, 0.44 mmol). The solution was warmed to -20°C over 1h. then recooled to -78°C. Methyl chloroformate (0.05 cm³, 0.60 mmol) was added and the solution warmed to room temperature over 1h. The solution was then quenched with saturated ammonium chloride solution (2 cm³) and extracted with diethyl ether (2 \times 10 cm³). The organic extracts were washed with water (2 \times 5 cm³) and saturated saline solution (2 \times 5 cm³) and dried with magnesium sulfate. The solvent was removed and the product distilled under reduced pressure to yield the title compound as a clear, sweet-smelling oil (62 mg, 56%); ν_{max} (liquid film) cm⁻¹ 2955-2857 (C-H), 2239 (C \equiv C), 1720 (C=O), 1256 (Si-CH₃), 1107 (Si-O-C), 1079 (C-O), 837 (Si-O-C); δ_H (CDCl₃) ppm 3.71 (3H, s, $\text{CH}_3\text{-O}$), 3.56 (2H, t, $^3J=7.1$ Hz, $\text{CH}_2\text{-O}$), 2.29 (2H, t, $^3J=7.4$ Hz, $\text{CH}_2\text{-C}\equiv\text{C}$), 1.47 (6H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-O}$), 0.84 (9H, s, 3 \times $\text{CH}_3\text{-C}$), 0.01 (6H, s, 2 \times $\text{CH}_3\text{-Si}$); m/z (C.I.) 285 (5%, MH⁺), 269 (4%), 253 (2%), 201

(85%), 183 (97%), 157 (90%), 125 (33%), 69 (100%).

Methyl 8-(hydroxy)oct-2-ynoate [104]⁽¹⁸¹⁾

The alkyne [103] (99 mg, 0.35 mmol) was heated at 85°C for 2.5h. in a solution of acetic acid, tetrahydrofuran and water (3:1:1, 2 cm³). The mixture was diluted with water (10 cm³), neutralized with sodium bicarbonate solution and extracted with diethyl ether (3 x 10 cm³). The organic extracts were combined, washed with water (2 x 5 cm³) and saline solution (2 x 5cm³) and dried with magnesium sulfate. The solvent was removed and the mixture distilled under reduced pressure to yield the title compound as a clear oil (59 mg, 99%); ν_{\max} (liquid film) cm⁻¹ 3400 (br, O-H), 2953-2970 (C-H), 2237 (C≡C), 1719 (C=O), 1076 (C-O); δ_H (CDCl₃) ppm 3.69 (3H, s, CH₃-O), 3.58 (2H, t, ³J=7.2 Hz, CH₂-O), 2.26 (2H, t, ³J=7.5 Hz, CH₂-C≡C), 2.05 (1H, br, OH), 1.48 (6H, m, CH₂-CH₂-CH₂-CH₂-O); m/z (C.I.) 171 (MH⁺, 100%), 139 (23%).

7-(Methoxycarbonyl)hept-6-ynoic acid [105]⁽¹⁸¹⁾

To a solution of the alcohol [104] (60 mg, 0.35 mmol) in acetone (1 cm³), was added Jones reagent (chromium(VI)oxide (2g) in water (3.28 cm³) and concentrated sulphuric acid (1.66 cm³)) until the orange colour of the oxidant persisted. The solution was stirred for

1h. at room temperature. Water (10 cm^3) was then added and the mixture extracted with diethyl ether ($3 \times 10\text{ cm}^3$). The combined organic portions were extracted with half saturated sodium carbonate solution ($3 \times 10\text{ cm}^3$). The combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with diethyl ether ($3 \times 10\text{ cm}^3$). The organic extracts were washed with water ($2 \times 10\text{ cm}^3$), and saline solution ($2 \times 10\text{ cm}^3$) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:3 to 3:1) to yield the title compound as a clear oil (37 mg, 57%); ν_{max} (CHBr_3) cm^{-1} 2950-2853 (C-H), 2237 ($\text{C}\equiv\text{C}$), 1710 (br, C=O, ester, C=O, acid), 1078 (C-O); δ_{H} (CDCl_3) ppm 5.5 (1H, br, O-H), 3.69 (3H, s, $\text{CH}_3\text{-O}$), 2.32 (4H, m, $\text{CH}_2\text{-C=O}$, $\text{CH}_2\text{-C}\equiv\text{C}$), 1.64 (4H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-C=O}$); m/z (C.I) 202 (100%, C.I.adduct, MNH_4^+), 185 (87%, MH^+), 167 (30%), 152 (32%), 139 (10%), 125 (10%), 124 (16%).

Ethyl 1,2,3,4-tetrahydro-2-(7-(methoxycarbonyl)hept-6-yn-1-oyl)isoquinoline-3-carboxylate [107].

A solution of the acid [105] (100 mg, 0.54 mmol) and cyanuric chloride (75.2 mg, 0.40 mmol) in dry acetone (5 cm^3) was stirred at room temperature. Triethylamine (54.8 mg, 0.54 mmol) was then added and the solution stirred at room temperature for 1h. The isoquinoline [67] (137 mg, 0.54 mmol) and sodium carbonate (57 mg, 0.54 mmol) were

added and the solution stirred for a further 14h. The triazine precipitate was removed by filtration and the solvent removed under reduced pressure. The remaining orange oil was taken up in diethyl ether (10 cm³) and dichloromethane (1 cm³) and washed with dilute hydrochloric acid (2 x 5 cm³), sodium carbonate (2 x 5 cm³), water (2 x 5 cm³) and saline solution (2 x 5 cm³) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9 to 1:1) to yield the title compound as a sweet-smelling yellow oil (116 mg, 58%); ν_{\max} (CHBr₃) cm⁻¹ 2955-2856 (C-H), 2236 (C \equiv C), 1707 (br, C=O, ester), 1641 (C=O, amide), 1080 (C-O); δ_H (CDCl₃) ppm (mixture of diastereoisomers) ppm 7.15 (8H, m, aromatic protons), 5.43 (1H, dd, ³J=3.8 Hz, ³J=5.7 Hz, CH-CH₂), 4.88 (1H, d, ²J=17.1 Hz, CHH-N), 4.80 (1H, dd, ³J=3.8 Hz, ³J=5.7 Hz, CH-CH₂), 4.67 (2H, s, CH₂-N), 4.52 (1H, d, ²J=17.1 Hz, CHH-N), 4.08 (4H, m, 2 x CH₂-O), 3.73 (6H, s, 2 x CH₃-O), 3.20 (4H, m, 2 x CH₂-CH), 2.51 (4H, m, 2 x CH₂-CO), 2.38 (4H, m, 2 x CH₂-C \equiv C), 1.75 (8H, m, 2 x CH₂-CH₂-CH₂-C=O), 1.24 (3H, t, ³J=7.1 Hz, CH₃-CH₂), 1.10 (3H, t, ³J=7.1 Hz, CH₃-CH₂); m/z (C.I) 372 (28%, MH⁺), 312 (12%), 298 (13%), 204 (70%), 132 (56%), 71 (100%).

1-(t-Butyldimethylsiloxy)-5-iodopentane [109]⁽¹⁸²⁾.

Method A.

The chloropentane [101] (0.52 g, 2.2 mmol), sodium iodide (3.3 g, 22 mmol) and acetone (25 cm³) were heated at reflux for 6h. The acetone was removed under reduced pressure to leave an orange oil. This was added to diethyl ether (100 cm³) and washed with water (2 x 50 cm³), 5% sodium thiosulfate solution (2 x 50 cm³) and saline solution (2 x 25 cm³). After drying with magnesium sulfate the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:49) to yield the title compound as a pale yellow oil (0.54 g, 75%); ν_{\max} (liquid film) cm⁻¹ 2953-2855 (C-H), 1256 (CH₃-Si), 110 (Si-O-C), 836 (Si-O-C); δ_{H} (CDCl₃) ppm 3.56 (2H, t, ³J=7.0 Hz, CH₂-O), 3.14 (2H, t, ³J=7.2 Hz, CH₂-I), 1.80 (2H, m, ³J=7.2 Hz, CH₂-CH₂-O), 1.43 (4H, m, CH₂-CH₂-CH₂-I), 0.84 (9H, s, 3 x CH₃-C), 0.01 (6H, s, 2 x CH₃-Si); m/z (C.I) 329 (5%, MH⁺), 271 (18%), 201 (16%), 197 (22%), 69 (100%).

Method B.

To a solution of t-butyldimethylsilylchloride (3 g, 20 mmol), sodium iodide (6 g, 40 mmol) and imidazole (1 g, 14.7 mmol) in acetonitrile (40 cm³) under an atmosphere of nitrogen in the dark, was added tetrahydropyran (7.1 cm³, 73 mmol). The solution was stirred at 50°C for 18h. Water (100 cm³) was then added and the solution extracted with diethyl ether (3 x 50 cm³). These extracts were

washed with 5% aqueous sodium thiosulfate solution (3 x 20 cm³), dilute hydrochloric acid (3 x 20 cm³) and saline solution (3 x 20 cm³). The solution was dried with magnesium sulfate. The solvent was removed under reduced pressure. The remaining oil was purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:24) to yield the title compound as a clear yellow oil (5.23 g, 80%).

11-Acetoxycarbonyl-1,2,3,4,5,10-hexahydroindeno[2,3-a]isoquinoline [111].

The isoquinoline [96] (70 mg, 0.2 mmol) was dissolved in acetic anhydride (10 cm³) and heated at 60°C for 2h. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9 to 1:1) to yield the title compound as an orange oil (2 mg, 43%); ν_{\max} (liquid film) cm⁻¹ 2920-2840 (C-H), 1780 (C=O), 1705 (C=O); δ_{H} (CDCl₃) ppm 7.25 (4H, m, aromatic protons), 4.91 (2H, s, CH₂-N), 4.40 (2H, s, CH₂-C-N), 2.70 (2H, t, CH₂-CH₂CH₂), 2.61 (2H, t, CH₂-CH₂-CH₂), 2.31 (3H, s, CH₃-C=O), 1.80 (4H, m, CH₂-CH₂-CH₂); m/z (E.I) 309 (47%, M+), 267 (95%), 250 (33%), 222 (100%); C₁₇H₁₇NO₂; Acc.Mass : Requires 267.12593, Found 267.12798.

1-(t-Butyldimethylsiloxy)-4-chlorobutane [113]⁽¹⁸³⁾

To a solution of 4-chloro-1-butanol (2.9g, 27 mmol) in dichloromethane (30 cm³) under an atmosphere of nitrogen, was added 1-(t-butyldimethylsilyl)imidazole (6.4g, 34 mmol). The mixture was stirred at room temperature for 18h. Dichloromethane (100 cm³) was then added and the solution was washed with dilute hydrochloric acid (3 x 50 cm³), saturated sodium hydrogen carbonate solution (3 x 50 cm³) and saline solution (2 x 50 cm³) and dried with magnesium sulfate. The solvent was removed and the product distilled under reduced pressure to yield the title compound as a clear sweet-smelling oil (5.9g, 98%); ν_{\max} (liquid film) cm⁻¹ 2956-2858 (C-H), 1256 (Si-CH₃), 1106 (Si-O-C), 837 (Si-O-C), 776 (C-Cl); δ_{H} (CDCl₃) ppm 3.60 (2H, t, ³J=7.2 Hz, CH₂-O), 3.53 (2H, t, ³J=7.4 Hz, CH₂-Cl), 1.81 (2H, m, CH₂-CH₂-O), 1.61 (2H, m, CH₂-CH₂-Cl), 0.84 (9H, s, 3 x CH₃-C), 0.01 (6H, s, 2 x CH₃-Si); m/z (C.I.) 240 (6%, C.I.adduct, MNH₄⁺), 223 (100%, MH⁺), 189 (4%), 187 (15%), 115 (4%), 91 (7%).

1-(t-Butyldimethylsiloxy)-4-iodobutane [114].⁽¹⁸⁴⁾

Method A.

To a solution of the chlorobutane [113] (6g, 26 mmol) in acetone (250 cm³), was added sodium iodide (39g, 260 mmol). The solution was heated at reflux for 16h. The acetone was removed under reduced pressure and the remaining oil taken up in diethyl ether (300 cm³) and

washed with water ($3 \times 50 \text{ cm}^3$), 5% aqueous sodium thiosulfate solution ($3 \times 50 \text{ cm}^3$) and brine ($3 \times 50 \text{ cm}^3$). The solution was dried with magnesium sulfate and the solvent removed under reduced pressure. The material was purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:49) to yield the title compound as a pale oil (6.5g, 77%); ν_{max} (liquid film) cm^{-1} 2955-2857 (C-H), 1256 (Si-CH₃), 1104 (Si-O-C), 936 (Si-O-C); δ_{H} (CDCl₃) ppm 3.59 (2H, t, $^3J=7.2 \text{ Hz}$, CH₂-O), 3.17 (2H, t, $^3J=7.5 \text{ Hz}$, CH₂-I), 1.85 (2H, m, CH₂-CH₂-O), 1.56 (2H, m, CH₂-CH₂-I), 0.84 (9H, s, $3 \times \text{CH}_3\text{-C}$), 0.01 (6H, s, $2 \times \text{CH}_3\text{-Si}$); m/z (E.I.) 315 (3%, MH⁺), 299 (17%), 257 (100%), 227 (4%), 185 (82%).

Method B.

To a solution of t-butyldimethylsilylchloride (3g, 20 mmol), sodium iodide (6g, 40 mmol) and imidazole (1g, 14 mmol) in acetonitrile (40 cm^3) under an atmosphere of nitrogen in the dark, was added tetrahydrofuran (59 cm^3 , 73 mmol). The solution was stirred at 55°C for 10h. Water (100 cm^3) was then added and the solution was extracted with ethyl acetate ($3 \times 50 \text{ cm}^3$). The combined organic extracts were then washed with aqueous 5% sodium thiosulfate solution ($3 \times 20 \text{ cm}^3$), dilute hydrochloric acid ($3 \times 20 \text{ cm}^3$) and saline solution ($3 \times 20 \text{ cm}^3$). The solution was dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified

by silica gel column chromatography (ethyl acetate : pet.ether, 1:24) to yield the title compound as a pale yellow oil (5.23g, 83%).

6-(t-Butyldimethylsiloxy)hex-1-yne [115]⁽¹⁸⁵⁾

To a solution of the iodobutane [114] (4.7g, 15 mmol) in dimethylformamide (50 cm³) under an atmosphere of nitrogen, was added 18% sodium acetylide solution in xylene (8g, 30 mmol). The solution was stirred at room temperature for 16h. Ice water (30 cm³) was slowly added and the resulting solution extracted with diethyl ether (3 x 100 cm³). The organic portions were combined and washed with water (3 x 50 cm³) and saline solution (3 x 50 cm³) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:49) to yield the title compound as a yellow oil (1.9g, 60%); ν_{\max} (liquid film) cm⁻¹ 2955-2857 (C-H), 1256 (Si-CH₃), 1107 (Si-O-C), 836 (Si-O-C), δ_H (CDCl₃) ppm 3.58 (2H, t, ³J=7.3 Hz, CH₂-O), 2.15 (2H, td, ³J=6.9 Hz, ⁴J=2.3 Hz, CH₂-C≡C), 1.88 (1H, t, ⁴J=2.3Hz, CH≡C), 1.51 (4H, m, CH₂-CH₂-CH₂-O), 0.84 (9H, s, 3 x CH₃-C), 0.01 (6H, s, 2 x CH₃-Si); m/z (C.I.) 213 (10%, MH⁺), 187 (92%), 97 (55%), 81 (66%), 57 (100%).

Methyl 7-(t-butyldimethylsiloxy)hept-2-ynoate [116]⁽¹⁸⁶⁾

To a solution of the alkyne [115] (3.18g, 15 mmol) in tetrahydrofuran (50 cm³) under an atmosphere of nitrogen at -78°C was added 1.6M butyllithium (10.3 cm³, 16.5 mmol). The solution was warmed to -20°C over 1h., then re-cooled to -78°C. Methyl chloroformate (2.13g, 22.5 mmol) was added and the mixture allowed to warm to room temperature and then stirred for 1h. The solution was quenched with saturated ammonium chloride solution (10 cm³). The solvent was removed under reduced pressure and diethyl ether (100 cm³) was added. The solution was then washed with water (2 x 50 cm³) and saline solution (2 x 50 cm³) and dried with magnesium sulfate. The solvent was removed and the product distilled under reduced pressure to yield the title compound as an orange, sweet-smelling oil (1.8g, 45%); ν_{max} (liquid film) cm⁻¹ 2956-2958 (C-H), 2239 (C≡C), 1720 (C=O), 1255 (Si-CH₃), 1100 (Si-O-C), 837 (Si-O-C); δ_{H} (CDCl₃) ppm 3.74 (3H, s, CH₃-O), 3.58 (2H, t, ³J=7.3 Hz, CH₂-O), 2.27 (2H, t, ³J=7.0 Hz, CH₂-C≡C), 1.55 (4H, m, CH₂-CH₂-CH₂-O), 0.84 (9H, s, 3 x CH₃-C), 0.01 (6H, s, CH₃-Si), m/z (C.I.) 288 (MNH₄⁺, C.I. adduct, 100%), 271 (48%, MH⁺).

Methyl 7-hydroxyhept-2-ynoate [117]⁽¹⁸⁷⁾

A solution of the alkyne [116] (1.62g, 6 mmol) in acetic acid (20 cm³), tetrahydrofuran (10 cm³) and water (10 cm³) was heated at 80°C for 1.5h. Water was added and the solution neutralised with sodium hydrogen carbonate. The

solution was extracted with diethyl ether ($3 \times 20 \text{ cm}^3$) and washed with water ($2 \times 10 \text{ cm}^3$) and saline solution ($2 \times 10 \text{ cm}^3$) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9) to yield the title product as a clear oil (926 mg, 99%); ν_{max} (liquid film) cm^{-1} 3400 (br, O-H), 2952-2870 (C-H), 2237 ($\text{C}\equiv\text{C}$), 1714 (C=O), 1258 (C-O), 1076 (C-O); δ_{H} (CDCl_3) ppm 3.71 (3H, s, $\text{CH}_3\text{-O}$), 3.60 (2H, t, $^3J=7.4 \text{ Hz}$, $\text{CH}_2\text{-OH}$), 2.32 (2H, t, $^3J=7.0 \text{ Hz}$, $\text{CH}_2\text{-C}\equiv\text{C}$), 1.72 (1H, br, O-H), 1.62 (4H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-O}$); m/z (C.I.) 174 (C.I.adduct, MNH_4^+ 100%), 157 (MH^+ , 48%), 125 (14%).

6-Methoxycarbonyl hex-5-ynoic acid [118].

To a solution of the alcohol [117] (100 mg, 0.6 mmol) in acetone (5 cm^3), was added Jones reagent (specified before) (5 cm^3). The solution was stirred at room temperature for 1h. Water (20 cm^3) was then added and the solution extracted with ethyl acetate ($4 \times 20 \text{ cm}^3$). The organic portions were combined and extracted with half saturated sodium carbonate solution ($4 \times 20 \text{ cm}^3$). These extracts were acidified with dilute hydrochloric acid and extracted with ethyl acetate ($3 \times 20 \text{ cm}^3$). The combined organic extracts were washed with water ($2 \times 20 \text{ cm}^3$) and saline solution ($2 \times 20 \text{ cm}^3$) and dried with magnesium sulfate. The solvent was removed and the product distilled under reduced pressure to yield the title compound

as a clear oil (55 mg, 54%). ν_{\max} (liquid film) cm^{-1} 3100 (br, O-H), 2956 (C-H), 2239 (C \equiv C), 1712 (br, C=O, ester, C=O, acid), 1080 (C-O, ester); δ_{H} (CDCl_3) ppm 9.51 (1H, br, O-H), 3.76 (3H, s, $\text{CH}_3\text{-O}$), 2.51 (4H, m, $\text{CH}_2\text{-C=O}$, $\text{CH}_2\text{C}\equiv\text{C}$), 1.60 (2H, m, $\text{CH}_2\text{-CH}_2\text{-C=O}$); m/z (E.I.) 171 (5%, M+), 153 (5%), 139 (26%), 138 (46%), 111 (47%), 110 (23%), 97 (70%), 94 (39%), 79 (100%), 66 (72%).

Ethyl 1,2,3,4-tetrahydro-2-(6-(methoxycarbonyl)hex-5-yn-1-oyl)-isoquinoline-3-carboxylate [120].

To a solution of the acid [118] (76.5 mg, 0.45 mmol) and cyanuric chloride (61.7 mg, 0.33 mmol) in dry acetone (5 cm^3) under an atmosphere of nitrogen, was added triethylamine (45.7 mg, 0.45 mmol). The solution was stirred at room temperature for 1.5h. Sodium carbonate (47.7 mg, 0.45 mmol) and the isoquinoline [67] (110 mg, 0.54 mmol) were then added and the solution stirred at room temperature for 15h. The triazine was then filtered off and the acetone removed under reduced pressure. The remaining red oil was then taken up in ethyl acetate (50 cm^3) and washed with dilute hydrochloric acid (2 x 20 cm^3), sodium carbonate solution (2 x 20 cm^3) and saline solution (2 x 20 cm^3). The solution was dried with magnesium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:19) to yield the title

compound as a sweet-smelling orange oil (94 mg, 63%); ν_{\max} (CHBr₃) cm^{-1} 2960-2850 (C-H), 2235 (C \equiv C), 1706 (C=O, ester), 1640 (C=O, amide), 1079 (C-O, ester); δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 7.22 (8H, m, aromatic protons), 5.38 (1H, dd, $^3J=6.0$ Hz, $^3J=3.7$ Hz, $\underline{\text{CH}}-\text{CH}_2$), 4.82 (1H, d, $^{\text{S}2}J=17.4$ Hz, $\underline{\text{CHH}}-\text{N}$), 4.78 (1H, m, $\underline{\text{CH}}-\text{CH}_2$), 4.64 (2H, s, $\underline{\text{CH}_2}-\text{N}$), 4.50 (1H, d, $^2J=17.4$ Hz, $\underline{\text{CHH}}-\text{N}$), 3.99 (4H, m, $2 \times \underline{\text{CH}_2}-\text{O}$), 3.69 (3H, s, $\underline{\text{CH}_3}-\text{O}$), 3.68 (3H, s, $\underline{\text{CH}_3}-\text{O}$), 3.17 (4H, m, $2 \times \underline{\text{CH}_2}-\text{CH}$), 2.58 (2H, t, $^3J=7.1$ Hz, $\underline{\text{CH}_2}-\text{C}=\text{O}$), 2.56 (2H, t, $^3J=6.9$ Hz, $\underline{\text{CH}_2}-\text{C}=\text{O}$), 2.43 (4H, m, $2 \times \underline{\text{CH}_2}-\text{C}\equiv\text{C}$), 1.93 (4H, m, $2 \times \underline{\text{CH}_2}-\text{CH}_2-\text{C}=\text{O}$), 1.05 (3H, t, $^3J=7.1$ Hz, $\underline{\text{CH}_3}-\text{CH}_2$), 1.01 (3H, t, $^3J=7.1$ Hz, $\underline{\text{CH}_3}-\text{CH}_2$); m/z (C.I.) 358 (36%, MH⁺), 326 (13%), 312 (31%), 298 (4%), 284 (25%), 252 (13%), 204 (100%), 132 (97%), 71 (57%).

1,2,3,4-Tetrahydro-2-(hept-1-oyl-5-yn-6-oic acid)-isoquinoline-3-carboxylic acid [121].

To a solution of the isoquinoline [120] (40 mg, 0.11 mmol) in tetrahydrofuran (5 cm^3) and water (5 cm^3) was added sodium hydroxide (11 mg, 0.27 mmol). The solution was stirred at room temperature for 2h. The solvent was then removed under reduced pressure and the remaining liquid made acidic with dilute hydrochloric acid. The solution was extracted with ethyl acetate (3×10 cm^3). These portions were combined and extracted with saturated sodium carbonate solution (3×10 cm^3). The solution was

acidified with dilute hydrochloric acid and extracted again with ethyl acetate ($3 \times 10 \text{ cm}^3$). The organic portions were then washed with water ($2 \times 10 \text{ cm}^3$) and brine ($2 \times 10 \text{ cm}^3$) and dried with sodium sulfate. The solvent was removed under reduced pressure to yield the title compound as a pale yellow oil (28.4 mg, 82%); ν_{max} (liquid film) cm^{-1} 3000 (br, O-H), 2230 ($\text{C}\equiv\text{C}$), 1710 ($\text{C}=\text{O}$, acid) 1645 ($\text{C}=\text{O}$, amide); δ_{H} (CDCl_3) ppm (mixture of diastereoisomers) 7.25 (4H, br, $4 \times \text{O-H}$), 7.10 (8H, m, aromatic protons), 5.34 (1H, dd, $^3J=6.0 \text{ Hz}$, $^3J=3.6 \text{ Hz}$, CH-CH_2), 4.81 (1H, d, $^2J=17.4 \text{ Hz}$, CH-H-N), 4.80 (1H, m, CH-CH_2), 4.64 (2H, s, $\text{CH}_2\text{-N}$), 4.50 (1H, d, $^2J=17.4 \text{ Hz}$, CHH-N), 3.15 (4H, m, $2 \times \text{CH}_2\text{-CH}$), 2.55 (4H, m, $2 \times \text{CH}_2\text{-C}=\text{O}$), 2.40 (4H, m, $2 \times \text{CH}_2\text{-C}\equiv\text{C}$), 1.87 (4H, m, $2 \times \text{CH}_2\text{-CH}_2\text{-CO}$); m/z (C.I.) 316 (MH^+ , 3%), 253 (52%), 246 (27%), 176 (100%), 132 (86%), 69 (43%).

10-Acetoxycarbonyl-1,2,3,4,9-pentahydropentaleno[2,3-a]isoquinoline [123].

The isoquinoline [121] (31.5 mg, 0.1 mmol) was dissolved in acetic anhydride (5 cm^3) and heated at 70°C for 3h. The solvent was removed under reduced pressure and the remaining oil purified by preparative plate chromatography (ethyl acetate : pet.ether, 1:1) to yield the title compound as an orange oil (10.9 mg, 37%); ν_{max} (liquid film) cm^{-1} 2930-2830 (C-H), 1790 ($\text{C}=\text{O}$), 1720 ($\text{C}=\text{O}$); δ_{H} (CDCl_3) ppm 7.30 (4H, m, aromatic protons), 4.97 (2H, t,

$^4J=2.2$ Hz, $\underline{\text{CH}_2\text{-N}}$), 4.40 (2H, s, $\underline{\text{CH}_2\text{-C-N}}$), 2.75 (4H, m, 2 \times $\underline{\text{CH}_2\text{-CH}_2\text{-CH}_2}$), 2.46 (2H, m, $\underline{\text{CH}_2\text{-CH}_2\text{-C=C}}$), 2.27 (3H, s, $\underline{\text{CH}_3\text{-C=O}}$); m/z (E.I.) 295 (23%, M+), 253 (64%), 236 (45%), 208 (100%); $\text{C}_{18}\text{H}_{17}\text{NO}_3$: Acc.Mass : Requires 295.12084, Found 295.12142.

t-Butyl 2,2-dimethyl-1,3-dioxen-4-one-6-acetate [128].

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (1 cm³, 4.73 mmol) in tetrahydrofuran (5 cm³) under an atmosphere of nitrogen at 0°C was added 1.6M butyllithium (2.95 cm³, 4.73 mmol). The solution was stirred for 30 minutes and then the temperature was reduced to -78°C. 2,2,6-Trimethyl-1,3-dioxen-4-one (0.61 cm³, 4.73 mmol) was slowly added and the solution warmed to 0°C over 10 minutes then cooled to -78°C and quenched with di-*t*-butyl dicarbonate (1.03g, 4.73 mmol) dissolved in tetrahydrofuran (2 cm³). After 1h at this temperature the solution was warmed to room temperature and saturated ammonium chloride solution (3 cm³) was added. The solvent was removed under reduced pressure and the remainder was taken up in ethylacetate (20 cm³) and washed with water (3 \times 3 cm³) and brine (3 \times 3 cm³) and dried with sodium sulfate. The solvent was removed under reduced pressure and the product purified by silica gel column chromatography (ethyl acetate : pet.ether, 1 : 9) to yield the title compound as a sweet smelling orange oil (815 mg, 76%) ; ν_{max} (liquid film) cm⁻¹ 2960 (C-H), 1725 (C=O), 1630 (C=C), 1270 (C-O-C); δ_{H}

(CDCl₃) ppm 5.22 (1H, s, $\underline{\text{CH}}\text{-C=O}$), 3.04 (2H, s, $\underline{\text{CH}}_2\text{-C=O}$), 1.56 (6H, s, $(\underline{\text{CH}}_3)_2\text{-C}$), 1.32 (9H, s, $(\underline{\text{CH}}_3)_3\text{-O}$); m/z (C.I.) 243 (MH⁺, 30%), 187 (100%), 169 (23%), 129 (88%); C₁₂H₁₈O₅ : Acc.mass : Requires 242.27122 , Found 242.27106.

2,2-Dimethyl-6-deuteriomethyl-1,3-dioxen-4-one [140].

To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (0.05 cm³, 0.24 mmol) in tetrahydrofuran (1.5 cm³) under an atmosphere of nitrogen was added 1.6M butyllithium (0.15 cm³, 0.24 mmol). After 30 minutes at 0°C the temperature was reduced to -78°C and 2,2,6-trimethyl-1,3-dioxen-4-one (0.03 cm³, 0.24 mmol). The temperature was raised to 0°C for 30 minutes and then recooled to -78°C. Deuterium oxide (0.01 cm³) was then added and the solution allowed to warm to room temperature. Ethyl acetate (2 cm³) was added and the solution washed with water (2 x 0.5 cm³) and brine (2 x 0.5 cm³) and dried with sodium sulfate. The material was purified by preparative plate chromatography (ethyl acetate : pet.ether, 1:4) to yield the title product as a clear oil (21.5 mg, 64%) ; δ_{H} (CDCl₃) ppm 5.24 (1H, t, $^3J=0.74\text{Hz}$, $\underline{\text{CH}}\text{-C=O}$), 1.97 (2H, m, $\underline{\text{CH}}_2\text{D}$), 1.69 (6H, s, $(\underline{\text{CH}}_3)_2\text{-C}$).

Mono and di-alkylated dioxenone mixture [129], [141], [142], [143], [144], [145].

To a stirred solution of 1,1,1,3,3,3-hexamethyldisilylamine (0.43cm^3 , 1.89 mmol) in tetrahydrofuran (12 cm^3) under an atmosphere of nitrogen at 0°C was added 1.6M butyllithium (1.18 cm^3 , 1.89 mmol). The solution was stirred for 30 minutes and then the temperature was lowered to -78°C . To this [88] (416 mg, 1.72 mmol) was added, after which the solution became clear red in colour. The solution was warmed to 0°C over 30 minutes. The temperature was then lowered to -78°C and propargyl bromide (0.21 cm^3 , 1.89 mmol) was added. After warming to room temperature over 2h the solution was quenched with saturated ammonium chloride solution and the solvent was removed under vacuum. The remaining oil was taken up in ethyl acetate (50 cm^3) and washed with water ($3 \times 20\text{ cm}^3$) and brine ($3 \times 20\text{ cm}^3$) and dried with sodium sulfate. The solvent was removed under reduced pressure and the product purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:10) to yield the title product as an orange oil (159 mg), n_{D}^{20} (liquid film) cm^{-1} 3300 (C-H), 2110 ($\text{C}\equiv\text{C}$), 1740-1720 (C=O , ester and lactone), 1635 (C=C), 1205, 1155 (C-O , ester and lactone); m/z (F.A.B.) 319 (67%, MH^+), 281 (25%, MH^+), 263 (100%), 167 (29%).

6-(But-3-yne)-2,2-dimethyl-1,3-dioxen-4-one [146].

Method A.

1.6M Butyllithium (8.8 cm³, 14.1 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (3 cm³, 14.1 mmol) in tetrahydrofuran (12 cm³) under an atmosphere of nitrogen at 0°C. After 30 minutes the temperature was reduced to -78°C and 2,2,6-trimethyl-1,3-dioxen-4-one (0.62 cm³, 4.7 mmol) was added. The temperature was then raised to 0°C for 30 minutes and then recooled to -78°C and hexamethylphosphoramide (5 cm³) and propargyl bromide (0.52 cm³, 4.7 mmol) were added, during which time the solution became cloudy grey/green in colour. After 5h the solution was allowed to warm to room temperature and quenched with saturated ammonium chloride solution. The solvent was removed under reduced pressure, ethyl acetate (30 cm³) was added and the solution washed with water (3 x 10 cm³) and brine (3 x 10 cm³) and dried with sodium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet. ether, 1:9) to yield the title compound as an orange oil (142 mg, 17%); ν_{max} (liquid film) cm⁻¹ 3290 (C \equiv C-H), 2980, 2910, 2820 (C-H), 2140 (C \equiv C), 1730-1700 (C=O), 1620 (C=C), 1270 (C-O-C); δ_{H} (CDCl₃) ppm 5.34 (1H, s, CH-C=O), 2.45 -2.38 (4H, m, CH₂-CH₂), 2.03 (1H, s, C \equiv C-H), 1.70 (6H, s, (CH₃)₂-O); m/z (C.I.) 181 (MH⁺, 100%), 123 (38%); C₁₀H₁₂O₃ : Acc.Mass : Requires 180.2035, Found 180.2033.

Method B.

To a solution of [157] (6.12g, 14.6 mmol) in tetrahydrofuran (100 cm³) was added 1.0M tetrabutylammonium fluoride (29.3 cm³, 29.3 mmol) which caused the solution to become violet in colour. The solution was stirred at room temperature for 3h after which time t.l.c. indicated that the reaction was complete. The solvent was removed under reduced pressure and the remaining blue oil taken up in ethyl acetate (100 cm³) and washed with dilute hydrochloric acid (3 x 20 cm³), water (3 x 20 cm³) and brine (3 x 20 cm³) and dried with sodium sulfate. The solvent was removed under reduced pressure and the product purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9) to yield the title compound a pale orange oil (1.74g, 66%).

2-(2-Propynoxy)tetrahydropyran [153]⁽¹⁶⁷⁾

To a solution of propargyl alcohol (10 cm³, 171.7 mmol) and 3,4-dihydro-2H-pyran (39.2 cm³, 429.9 mmol) in dichloromethane (100 cm³) at 0°C was added *p*-toluenesulphonic acid monohydrate (164 mg, 0.86 mmol). The solution became a clear purple colour and was stirred for 1h. at room temperature. The solution was then washed with saturated sodium hydrogen carbonate solution (2 x 50 cm³), water (2 x 50 cm³) and brine (2 x 50 cm³) and dried with sodium sulfate. The solvent was removed and the product distilled under reduced pressure to yield the title compound as a clear sweet-smelling oil (23.5 g,

98%); ν_{\max} (liquid film) cm^{-1} 3280 (C=C-H), 2100 (C \equiv C), δ_{H} (CDCl_3) ppm 4.81 (1H, t, $^3J=3.3$ Hz, O-CH O), 4.27 (1H, dd, $^2J=15.8$ Hz, $^4J=2.4$ Hz, CHH-C \equiv C), 4.22 (1H, dd, $^2J=15.8$ Hz, $^4J=2.4$ Hz, CHHC \equiv C), 3.82 (1H, m, O-CHH-CH $_2$), 3.53 (1H, m, O-CHH-CH $_2$), 2.40 (1H, t, $^4J=2.4$ Hz, CH-C \equiv C), 1.8-1.5 (6H, m, CH $_2$ -CH $_2$ -CH $_2$ -CH); m/z (E.I.) 139 (10%), 101 (7%), 85 (100%), 55 (61%), 39 (77%); $\text{C}_8\text{H}_{11}\text{O}_2$: Acc.Mass : Calculated 139.07590, Found 139.07595.

2-(3-(*t*-Butyldiphenylsilyl)-2-propynoxy)tetrahydropyran
[154].

To a stirred solution of 1.6M butyllithium (5.92 cm^3 , 9.4 mmol) in tetrahydrofuran (10 cm^3) under an atmosphere of nitrogen at -78°C was added 2-(2-propynoxy)tetrahydropyran (1.32g, 9.4 mmol). After 30 minutes *t*-butyldiphenylsilyl chloride (2.4 cm^3 , 9.4 mmol) was added and stirring was continued at this temperature for a further 2h. The solution was warmed to room temperature over 1h and then quenched with saturated ammonium chloride solution. The solvent was removed under vacuum. The remainder was taken up in dichloromethane (50 cm^3) and washed with water (2 x 20 cm^3) and brine solution (2 x 20 cm^3) and dried with sodium sulfate. The solvent was removed under reduced pressure and the crude product purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:19) to yield the title compound as a clear sweet-smelling oil (3.40g, 95%); ν_{\max} (liquid film) cm^{-1} 2150 (C \equiv C), 1110

(Si-phenyl); δ_H ($CDCl_3$) ppm 7.79 (4H, m, meta aromatic protons), 7.40 (6H, m, ortho and para aromatic protons), 4.81 (1H, t, $^3J=3.3$ Hz, O-CH-O), 3.98 (1H, d, $^2J=15.8$ Hz, CHH-C \equiv C), 3.94 (1H, d, $^2J=15.8$ Hz, CHH-C \equiv C), 3.81 (1H, m, O-CHH-CH $_2$), 3.51 (1H, m, O-CHH-CH $_2$), 1.8-1.5 (6H, m, CH $_2$ -CH $_2$ -CH), 1.11 (9H, s, 3 \times (CH $_3$) $_3$ -C) m/z (E.I.) 321 (57%), 221 (55%), 139 (100%), 123 (28%), 115 (46%), 57 (69%); C $_{20}$ H $_{21}$ O $_2$ Si : Acc.Mass : Requires 321.13108, Found 321.12763.

3-(*t*-Butyldiphenylsilyl)-2-propyn-1-ol [155]⁽¹⁸⁸⁾

A solution of 2-(3-(*t*-butyldiphenylsilyl)-2-propynoxy)tetrahydropyran (1g, 2.64 mmol) in acetic acid (8 cm 3), tetrahydrofuran (4 cm 3) and water (1 cm 3) was stirred at 50°C for 4h. The solvent was removed under vacuum and the remainder was taken up in ethyl acetate (30 cm 3) and washed with saturated sodium hydrogen carbonate solution (2 \times 20 cm 3) and brine (2 \times 20 cm 3) and dried with sodium sulfate. The solvent was removed under reduced pressure and the crude product purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:9) to yield the title compound as a sweet-smelling orange oil (690 mg, 89%); ν_{max} (liquid film) cm $^{-1}$ 3400 (br, O-H), 2150 (C \equiv C), 1100 (Si-phenyl); δ_H ($CDCl_3$) ppm 7.81 (4H, m, meta aromatic protons), 7.41 (6H, m, ortho and para aromatic protons), 4.44 (2H, s, CH $_2$ -C \equiv C), 1.91 (1H, s, O-H), 1.12 (9H, s, 3 \times CH $_3$ -C); m/z (E.I.) 237

(100%), 115 (43%); $C_{15}H_{13}OSi$: Acc.Mass : Calculated 237.07357, Found 237.07522.

1-Bromo-3-(*t*-butyldiphenylsilyl)-2-propyne [156].

To a solution of 3-(*t*-butyldiphenylsilyl)-2-propyne-1-ol (1g, 3.4 mmol) and pyridine (0.01 cm³) in dry ether (4 cm³) under an atmosphere of nitrogen was added phosphorus tribromide (0.13 cm³, 1.3 mmol) dropwise. The solution was stirred at room temperature for 2h. It was then poured onto ice. Ether (10 cm³) was then added and the organic portion was washed with saturated sodium hydrogen carbonate solution (2 x 5 cm³), water (2 x 5 cm³) and brine (2 x 5 cm³) and dried with sodium sulfate. The solvent was removed under reduced pressure and the product was purified by silica gel column chromatography (ethyl acetate : petroleum, 1:19) to yield the title compound as a yellow oil (1.02g, 90%); v_{max} (liquid film) cm⁻¹ 2150 (C≡C), 1490 (Si-phenyl), 700 (C-Br); δ_H (CDCl₃) ppm 7.81 (4H, m, meta aromatic protons), 7.42 (6H, m, ortho and para aromatic protons), 4.08 (2H, s, $\underline{CH_2}$ -C≡C), 1.15 (9H, s, 3 x $\underline{CH_3}$ -Si); m/z (C.I.) 301 (76%), 300 (18%), 299 (73%), 277 (27%), 239 (44%), 199 (100%); $C_{15}H_{12}BrSi$: Acc.Mass : Requires 298.98916, Found 298.99388.

6-(4-(*t*-Butyldiphenylsilyl)-3-butyne)-2,2-dimethyl-1,3-dioxen-4-one [157].

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.69 cm³, 3.3 mmol) in tetrahydrofuran (5 cm³) under an atmosphere of nitrogen at 0°C was added 1.6M butyllithium (2.06 cm³, 3.3 mmol). The solution was stirred for 30 minutes and the temperature was then reduced to -78°C. 2,2,6-Trimethyl-1,3-dioxen-4-one (0.39 cm³, 3.0 mmol) was added dropwise and the solution warmed to 0°C over 30 minutes. It was then cooled to -78°C and 1-bromo-3(*t*-butyldiphenylsilyl)-2-propyne (745 mg, 2.1 mmol) was added. The solution was allowed to warm to room temperature over 2h. The solution was quenched with saturated ammonium chloride solution (5 cm³) and the solvent was removed under vacuum. The remainder was taken up in ethyl acetate (25 cm³) and washed with water (2 x 10 cm³) and brine solution (2 x 10 cm³) and dried with sodium sulfate. The solvent was removed under reduced pressure and the product purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:19) to yield the title compound as a colourless oil (709 mg, 81%); ν_{max} (liquid film) cm⁻¹ 2160 (C≡C), 1735 (C=O), 1630 (C=C), 1200 (C-O-C); m/z (+F.A.B.) 419 (8%, MH⁺), 361 (49%), 341 (100%), 303 (22%), 283 (26%); C₂₂H₂₁O₃Si (- *t*-butyl group) .
 Acc.Mass : Requires 361.1260, Found 361.1266.

Methods towards the acylation of 6-(4-(*t*-butyldiphenylsilyl)-3-butyne)-2,2-dimethyl-1,3-dioxen-4-one.

To a stirred solution of the dioxenone [157] (100 mg,

0.239 mmol) in tetrahydrofuran (3 cm³) under an atmosphere of nitrogen was added sodium hydride (6.8 mg, 0.286 mmol). After 2h stirring at room temperature di-*t*-butyl dicarbonate (52.2 mg, 0.239 mmol) was added. The solution was stirred for 24h but mini work up and t.l.c at this stage revealed only starting material to be present.

To a stirred solution of 1,1,1,3,3,3,-hexamethyldisilazane (1 cm³, 0.47 mmol) in tetrahydrofuran (2 cm³) under an atmosphere of nitrogen at -78°C, was added 1.6M butyllithium (0.29 cm³, 0.47 mmol). After raising the temperature to 0°C for 30 minutes, it was reduced to -78°C and the dioxenone [157] (98 mg, 0.235 mmol) was added. The temperature was raised to 0°C for 30 minutes then re-cooled to -78°C and ethyl chloroformate (0.022 cm³, 0.235 mmol) was added. After stirring at this temperature for 2h the solution was warmed to room temperature over 1h. Work up showed that only starting material was present.

To a stirred solution of the dioxenone [157] (100 mg, 0.239 mmol) in tetrahydrofuran (3 cm³) under an atmosphere of nitrogen at room temperature was added sodium hydride (6.8 mg, 0.239 mmol). After 2h a pellet of solid carbon dioxide was added. Mini work up at this stage revealed only starting material. A further pellet of carbon dioxide was added but work up after 5h (quenching with saturated ammonium chloride solution) again revealed only starting material to be present.

6-(But-4-(*t*-butyldiphenylsilyl)-1-deuterio-3-yne)-2,2-dimethyl-1,3-dioxen-4-one [159].

To a stirred solution of 1,1,1,3,3,3-hexamethyldisilylazine (0.05 cm^3 , 0.24 mmol) in tetrahydrofuran (1.5 cm^3) under an atmosphere of nitrogen at 0°C was added 1.6M butyllithium (0.15 cm^3 , 0.24 mmol). The solution was stirred for 30 minutes and the temperature was then lowered to -78°C . To this the dioxenone [157] (100 mg, 0.24 mmol) was added and the solution warmed to 0°C over 30 minutes then recooled to -78°C . Deuterium oxide (0.01 cm^3) was then added and the solution warmed to room temperature. Ethyl acetate (1.5 cm^3) was added and the solution washed with brine ($2 \times 0.5\text{ cm}^3$) and dried with sodium sulfate. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate, pet. ether, 1:19) to yield the title compound as a colourless oil (93.7 mg, 83%), δ_{H} (CDCl_3) ppm 7.78-7.74 (4H, m, meta aromatic protons), 7.39-7.34 (4H, m, ortho and para aromatic protons), 5.40 (1H, s, $\text{CH}=\text{C}=\text{O}$), 2.70-2.65 (1H, m, $\text{CH}-\text{CH}_2$), 2.55 (2H, d, $^3J=6.2\text{ Hz}$, CH_2-CHD), 1.66 (6H, s, $(\text{CH}_3)_2-\text{C}=\text{O}$), 1.07 (9H, s, $(\text{CH}_3)_3-\text{C}-\text{Si}$).

Ethyl 2-(hept-6-yne-1,3-dione)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate [163].

A solution of the isoquinoline ester [67] (200 mg, 0.97

mmol) and the dioxenone [146] (175 mg, 0.97 mmol) in xylene (5 cm³) was refluxed for 3h during which time the solution became orange in colour. The solvent was removed under reduced pressure and the remaining oil purified by preparative plate chromatography (ethyl acetate : pet.ether, 1:1) to yield the title compound as a yellow oil (200 mg, 63%) ; ν_{\max} (liquid film) cm⁻¹ 3260 (\equiv C-H), 2980-2880 (C-H), 2230 (C \equiv C), 1740-1720 (C=O, ester and ketone), 1630 (C=O, amide), 1340, 1050 (C-O) ; δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 7.23-7.10 (8H, m, aromatic protons), 5.47 (1H, dd, ³J=5.8 Hz, ³J=3.3 Hz, $\underline{\text{CH}}-\text{CH}_2$), 4.93 (1H, d, ²J=17.6 Hz, $\underline{\text{CHH}}-\text{N}$), 4.84 (1H, dd, ³J=5.5 Hz, ³J=3.1 Hz, $\underline{\text{CH}}-\text{CH}_2$), 4.67 (2H, s, $\underline{\text{CH}_2}-\text{N}$), 4.15-4.01 (4H, m, 2 \times $\underline{\text{CH}_2}-\text{O}$), 3.67 (2H, s, $\underline{\text{CH}_2}-\text{C}=\text{O}$), 3.62 (2H, s, $\underline{\text{CH}_2}-\text{C}=\text{O}$), 3.41-3.10 (4H, m, 2 \times $\underline{\text{CH}_2}-\text{C}-\text{N}$), 2.41 (2H, t, ³J=7.1 Hz, $\underline{\text{CH}_2}\underline{\text{CH}_2}-\text{C}=\text{O}$), 2.38 (2H, t, ³J=7.1 Hz, $\underline{\text{CH}_2}-\underline{\text{CH}_2}-\text{C}=\text{O}$), 2.24-2.16 (4H, m, 2 \times $\underline{\text{CH}_2}-\text{C}\equiv\text{C}$), 2.06 (1H, t, ⁴J=2.3 Hz, $\underline{\text{CH}}-\text{C}\equiv\text{C}$), 2.03 (1H, t, ⁴J=2.1 Hz, $\underline{\text{CH}}-\text{C}\equiv\text{C}$), 1.17 (3H, t, ³J=7.1 Hz, $\underline{\text{CH}_3}-\underline{\text{CH}_2}$), 1.13 (3H, t, ³J=7.1 Hz, $\underline{\text{CH}_3}-\underline{\text{CH}_2}$) ; m/z (E.I.) 327 (M⁺, 7%), 204 (78%), 132 (100%) ; C₁₉H₂₁NO₄ : Acc. Mass : Requires 327.14706, Found 327.14102.

2-(Hept-6-yne-1,3-dione)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid [164].

To a solution of the isoquinoline ester [163] (100mg, 0.3 mmol) in tetrahydrofuran (3 cm³) and water (3 cm³) was

added sodium hydroxide (30 mg, 0.75 mmol). After stirring at room temperature for 1.5h the solvent was removed under reduced pressure and the solution was made acidic with dilute hydrochloric acid. This was extracted with ethyl acetate ($3 \times 10 \text{ cm}^3$). These portions were combined and extracted with sodium carbonate solution ($3 \times 10 \text{ cm}^3$). These combined extracts were acidified with dilute hydrochloric acid and extracted again with ethyl acetate ($3 \times 10 \text{ cm}^3$). The combined organic portions were washed with water ($3 \times 5 \text{ cm}^3$) and saline solution ($3 \times 5 \text{ cm}^3$) and dried with sodium sulfate. The solvent was removed and the product distilled under reduced pressure to yield the title compound as a pale yellow oil (74.6 mg, 83%); ν_{max} (liquid film) cm^{-1} 3200-2700 (C-H and O-H), 2230 (C \equiv C), 1720-1710 (C=O, ketone and acid), 1635 (C=O, amide), 1340, 1050 (C-O); δ_{H} (CDCl_3) ppm (mixture of diastereoisomers) 7.25-7.12 (2H, m, aromatic protons), 6.99 (2H, br, 2 \times O-H), 5.52 (1H, dd, $^3J=6.2 \text{ Hz}$, $^3J=3.5 \text{ Hz}$, $\text{CH}-\text{CH}_2$), 4.92 (1H, d, $^2J=17.6 \text{ Hz}$, $\text{CHH}-\text{N}$), 4.86 (1H, m, $\text{CH}-\text{CH}_2$), 4.67 (2H, s, CH_2-N), 4.51 (1H, d, $^2J=17.6 \text{ Hz}$, $\text{CHH}-\text{N}$), 3.68 (2H, s, $\text{CH}_2-\text{C}=\text{O}$), 3.64 (2H, s, $\text{CH}_2-\text{C}=\text{O}$), 3.45-3.12 (4H, m, 2 \times $\text{CH}_2-\text{C}-\text{N}$), 2.41 (2H, t, $^3J=6.9 \text{ Hz}$, $\text{CH}_2\text{CH}_2-\text{C}=\text{O}$), 2.38 (2H, t, $^3J=7.1 \text{ Hz}$, $\text{CH}_2-\text{CH}_2-\text{C}=\text{O}$), 2.25-2.15 (4H, m, 2 \times $\text{CH}_2-\text{C}\equiv\text{C}$), 2.05 (1H, t, $^4J=2.4 \text{ Hz}$, $\text{CH}-\text{C}\equiv\text{C}$), 2.02 (1H, t, $^4J=2.1 \text{ Hz}$, $\text{CH}-\text{C}\equiv\text{C}$); m/z (C.I) 300 (MH^+ , 100%), 162 (33%).

Ethyl 2-(butan-1,3-dione)-1,2,3,4-tetrahydroisoquinoline-

3-carboxylate [167].

Method A.

A solution of the isoquinoline ester [67] (0.5g, 2.43 mmol) and the dioxenone [126] (0.31 cm³, 2.43 mmol) was refluxed in toluene (10 cm³) for 5.5h, during which time the solution became dark brown in colour. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:1) to yield the title compound as a pale orange oil (433 mg, 62%) ; ν_{\max} (liquid film) cm⁻¹ 2880-2820 (C-H), 1715 (C=O, ester), 1620 (C=O, amide), 1020 (C-O) ; δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 7.23-7.12 (8H, aromatic protons), 5.47 (1H, dd, ³J=5.86Hz, CH-CH₂), 4.91 (1H, d, ²J=17.6Hz, CHH-N), 4.33 (1H, dd, ³J=5.5 Hz, ³J=2.9Hz, CH-CH₂), 4.65 (2H, s, CHS₂-N), 4.55 (1H, d, ²J=17.6 Hz, CHH-N), 4.12-4.00 (4H, m, 2 × CH₂-O), 3.68 (2H, s, CH₂-C=O), 3.61 (2H, s, CH₂-C=O), 3.38-3.09 (4H, m, 2 × CH₂-C-N), 2.32 (3H, s, CH₃-C=O), 2.30 (3H, s, CH₃-C=O), 1.13 (3H, t, ³J=6.7 Hz, CH₃-CH₂), 1.08 (3H, t, ³J=7.3 Hz, CH₃-CH₂) ; m/z (E.I.) 289 (18%), 204 (81%), 132 (1100%) ; C₁₆H₁₉NO₄ : Acc.Mass : Requires 289.3304 , Found 289.3330.

Method B.

A solution of the isoquinoline ester [67] (0.5g, 2.43

mmol) and the dioxenone [126] (0.31 cm^3 , 2.43 mmol) in xylene (10 cm^3) was refluxed for 1h, during which time the solution became orange in colour. The solvent was then removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:1) to yield the title compound as a pale orange oil (586 mg, 83%).

Ethyl 4,9-dihydro-3-methyl-1-phenylpyrrolo[1,2-*b*]isoquinoline-2-carboxylate [168].

The isoquinoline acid [91] (159 mg, 0.9 mmol) was added to a stirred solution of ethyl phenyl propiolate (37 ml, 2.25 mmol) in acetic anhydride (10 cm^3). The solution was heated at 80°C for 8h. During this time the solution became yellow in colour. The solvent was removed under reduced pressure and the remaining oil was purified by silica gel column chromatography (ethyl acetate: pet ether, 1:9 to 1:4) to yield the title compound as a yellow oil (166 mg, 56%): V_{max} (liquid film) cm^{-1} 2950 (C-H), 1680 (C=O), 1050 (C-O), 740 (C-H); δ_{H} (CDCl_3) ppm 7.42-7.21 (9H, m, aromatic protons), 5.01 (2H, s, $\text{CH}_2\text{-N}$), 4.10-4.057 (2H, m, $\text{CH}_2\text{-CH}_3$), 3.93 (2H, s, br, $\text{CH}_2\text{-C-N}$), 2.66 (3H, s, $\text{CH}_3\text{-C-N}$), 1.09-1.01 (3H, m, $\text{CH}_3\text{-CH}_2\text{-O}$); m/z (E.I) 331 (M+, 10%), 316 (17%), 302 (7%), 271 (12%), 258 (12%), 105 (96%), 77 (100%), 29 (96%); $\text{C}_{20}\text{H}_{16}\text{N}_2$: Acc.Mass : Requires 331.1572, Found 331.1571.

1-Acetyl-4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline

[169].

The isoquinoline acid [91] (159 mg, 0.9 mmol) was added to a solution of 3 butyn-2-one (1.8 cm³, 2.25 mmol) in acetic anhydride (10 cm³). The mixture was stirred and heated at 130°C for 1.5h. The solvent was removed under reduced pressure and the remaining material purified by silica gel preparative plate chromatography (ethyl acetate : pet.ether, 1:3) to yield the title compound as an orange oil (144 mg, 71 %); ν_{\max} (liquid film) cm⁻¹ 2940 (C-H), 1660 (C=O), 745 (C-H); δ_H (CDCl₃) ppm 7.32-7.24 (4H, m, aromatic protons), 6.32 (1H, q, ⁴J=0.9 Hz, CH=CCH₂), 4.95 (2H, s, CH₂-N), 4.44 (2H, s, br, CH₂-C-H), 2.59 (3H, d, ⁴J=0.9 Hz CH₂-C-N), 2.32 (3H, s, CH₂-C=O); m/z (E.I) 225 (M⁺, 100%), 182 (24%); C₁₅H₁₃NO; Acc.Mass : Requires 225.11576, Found 225.11296.

2-Cyano-4,9-dihydro-3-methyl-1-phenylpyrrolo[1,2-b]isoquinoline [173].

A solution of the tetrahydroisoquinoline acid [91] (28 mg, 0.5 mmol) and benzylidenemalononitrile (185 mg, 1.2 mmol) in acetic anhydride (25 cm³) was heated to reflux under an atmosphere of nitrogen for 2h. During this time the solution became orange. The solvent was removed under reduced pressure and the material purified by silica gel column chromatography (ethyl acetate : pet ether, 1:4) to yield the title compound as an orange oil (109 mg, 77%);

ν_{\max} (CHBr₃) cm⁻¹ 2214 (C≡N), 743 (C-H); δ_{H} (CDCl₃) ppm 7.45-7.27 (9H, m, aromatic protons), 5.02 (2H, brs, CH₂-N), 4.23 (2H, brs, CH₂-C=C), 2.37 (3H, s, CH₃-C=C); m/z (E.I) 284 (100%, M+), 269 (74%), 207 (7%); C₂₀H₁₆N₂ : Acc.Mass : Requires 284.1313, Found 284.1314.

1,2,3,4-Tetrahydro-2-acetyl-isoquinoline-3-carboxylic acid [174].

To a solution of the isoquinoline [91] (354 mg, 2 mmol) in dilute sodium hydroxide solution (2 cm³), was added acetic anhydride (2 cm³). The solution was stirred for 1h. at room temperature. Dilute hydrochloric acid (2 cm³) was added and the solution extracted with ethyl acetate (3 x 5 cm³) and washed with water (2 x 5 cm³) and saline solution (2 x 5 cm³) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the product crystallized from ethanol to yield the title compound as a white solid (407 mg, 93%); ν_{\max} (nujol mull) cm⁻¹ 2600 (O-H), 1725 (C=O, acid), 1590 (C=O, amide); δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 12.44 (2H, br, s, 2 x O-H), 7.20 (9H, m, aromatic protons), 5.17 (1H, dd, ³J=5.7 Hz, ³J=3.6 Hz, CH-CH₂), 4.85 (1H, d, ⁵J=17.5 Hz, CHH-N), 4.63 (1H, m, CH-CH₂), 4.60 (1H, d, ²J=15.0 Hz, CHH-N), 4.54 (1H, d, ²J=15.0 Hz, CHH-N), 4.43 (1H, d, ²J=17.5 Hz, CHH-N), 3.20 (4H, m, 2 x CH₂-CH), 2.14 (3H, s, CH₃-C=O), 2.08 (3H, s, CH₃-C=O); m/z (C.I.) 220 (26%, MH+), 176 (26%), 132 (57%), 85

(100%).

1,2,3,4-Tetrahydro-2-(benzylformate)-isoquinoline-3-carboxylic acid [177].

To a solution of the isoquinoline [91] (88 mg, 0.5 mmol) in dilute sodium hydroxide solution (2 cm³) under an atmosphere of nitrogen at 0°C was added benzyl chloroformate (93.8 mg, 0.55 mmol). The solution was stirred for 1h. and then made acidic with dilute hydrochloric acid (2 cm³) and extracted with ethyl acetate (3 x 5 cm³). The combined organic extracts were then washed with saturated sodium hydrogen carbonate solution (2 x 3 cm³), water (2 x 3 cm³) and saturated saline solution (2 x 3 cm³) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the remaining oil purified by silica gel column chromatography (ethyl acetate : pet.ether, 1:3) to yield the title compound as a sweet-smelling clear oil (86 mg, 58%); ν_{max} (CHBr₃) cm⁻¹ 3000 (br, O-H) 1716 (C=O, acid) 1697 (C=O, amide); δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 7.67 (2H, br, 2 x O-H), 7.4-7.0 (18H, m, aromatic protons), 5.19 (5H, m, 2 x CH₂-O, CH-CH₂), 4.96 (1H, dd, ³J=5.7 Hz, ³J=5.1 Hz, CH-CH₂), 4.77 (1H, d, ²J=15.5 Hz, CHH-N), 4.55 (3H, m, CH₂-N, CHH-N), 3.20 (4H, m, 2 x CH₂-C-N); m/z (PDTOF) 334 (17%, MNa+), 312 (9%, MH+), 266 (21%), 176 (22%), 130 (63%), 91 (100%).

1,2,3,4-Tetrahydro-2-(carboxaldehyde)-isoquinoline-3-carboxylic acid [178]⁽¹⁸⁹⁾

A solution of formic acid (0.55g, 12 mmol) and acetic anhydride (1.02g, 10 mmol) was heated under an atmosphere of nitrogen at 60°C for 1h. The isoquinoline [91] (104 mg, 0.59 mmol) was added and the mixture heated at 60°C for 2h. The solvent was removed under reduced pressure and the remaining oil purified by preparative plate chromatography (ethyl acetate : pet.ether, 3:1) to yield the title compound as white crystals (32 mg, 26%); ν_{\max} (CHBr₃) cm^{-1} 1740 (C=O, acid), 1669 (C=O, amide); δ_{H} (CDCl₃) ppm (mixture of diastereoisomers) 9.83 (2H, br, 2 \times O-H), 8.32 (1H, s, H-C=O), 8.23 (1H, s, H-C=O), 7.20 (8H, m, aromatic protons), 5.19 (1H, dd, $^3J=5.8$ Hz, $^2J=5.0$ Hz, CH-CH₂), 4.96 (1H, d, $^2J=16.7$ Hz, CHH-N), 4.70 (1H, d, $^2J=15.4$ Hz, CHH-N), 4.65 (1H, m, CH-CH₂), 4.55 (1H, d, $^2J=15.5$ Hz, CHH-N), 4.46 (1H, d, $^2J=16.7$ Hz, CHH-N), 3.21 (4H, m, 2 \times CH₂-CH); m/z (C.I.) 206 (71%, MH⁺), 160 (32%), 132 (5%), 79 (100%).

Dimethyl-4,9-dihydropyrrolo[1,2-*b*]isoquinoline-1,2-dicarboxylate [180].

A solution of the amide [178] (26 mg, 0.126 mmol) and dimethylacetylene dicarboxylate (21 mg, 0.152 mmol) in acetic anhydride (5 cm^3) under an atmosphere of nitrogen was heated at 70°C for 1h. The solvent was removed under

reduced pressure and the remaining oil purified by preparative plate chromatography (ethyl acetate : pet.ether, 1:3) to yield the title compound as a yellow oil (19 mg, 54%); ν_{\max} (CHBr₃) cm^{-1} 1718 (C=O), 1064 (C-O); δ_{H} (CDCl₃) ppm 7.25 (4H, m, aromatic protons), 6.39 (1H, s, CH-N), 5.06 (2H, s, CH₂-N), 4.30 (2H, s, CH₂-C-N), 3.88 (3H, s, CH₃-O), 3.82 (3H, s, CH₃-O); m/z (C.I) 286 (100%, MH+), 254 (100%).

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